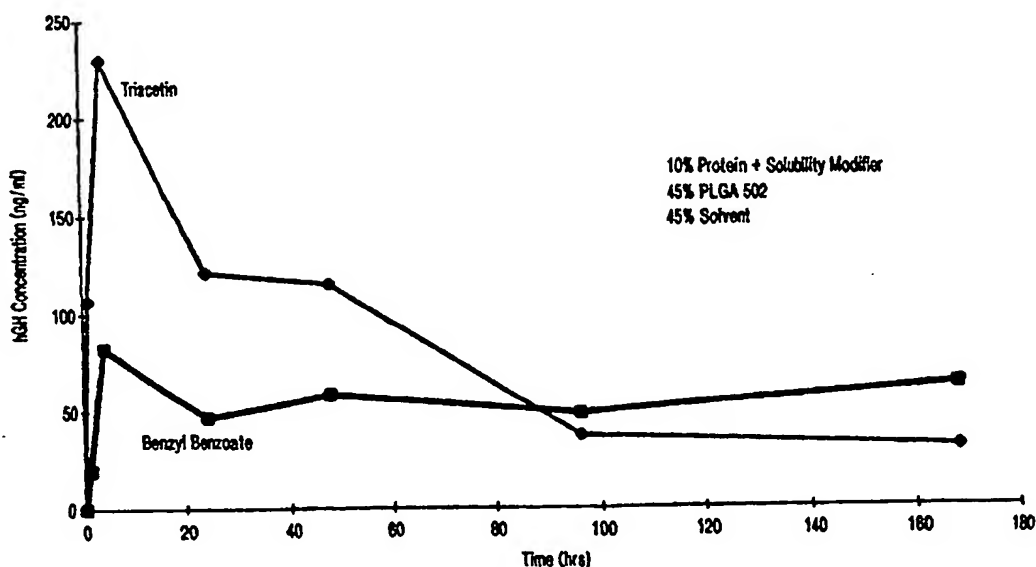




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 47/34		A2	(11) International Publication Number: WO 98/27963
			(43) International Publication Date: 2 July 1998 (02.07.98)
(21) International Application Number: PCT/US97/23659 (22) International Filing Date: 18 December 1997 (18.12.97) (30) Priority Data: 60/033,439 20 December 1996 (20.12.96) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRODBECK, Kevin, J. [US/US]; 2383 South Court Street, Palo Alto, CA 94301 (US). GAYNOR-DUARTE, Ann, T. [US/US]; 13063 Broadway Terrace, Oakland, CA 94611 (US). SHEN, Theodore, T. [US/US]; 18 Dockside Circle, Redwood City, CA 94065 (US). (74) Agents: DHUEY, John, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	

(54) Title: GEL COMPOSITION AND METHODS



(57) Abstract

Methods and compositions for systemically or locally administering by implantation a beneficial agent to a subject are described, and include, for example, compositions having burst indices of 8 or less for systemic applications and systems releasing 10 % or less of the total dose of beneficial agent in the first 24 hours after implantation for local applications. The compositions include a biocompatible polymer, a biocompatible solvent having low water miscibility that forms a viscous gel with the polymer and limits water uptake by the implant, and a beneficial agent.

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GEL COMPOSITION AND METHODS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a gel composition that can be implanted into a desired location and which can provide controlled release of a beneficial agent. The present invention also relates to methods of controlling release of a beneficial agent from a composition.

Description of the Related Art

Biodegradable polymers have been used for many years in medical applications. Illustrative devices composed of the biodegradable polymers include sutures, surgical clips, staples, implants, and sustained release drug delivery systems. The majority of these biodegradable polymers have been based upon glycolide, lactide, caprolactone, and copolymers thereof.

The biodegradable polymers can be thermoplastic materials which means that they can be heated and formed into various shapes such as fibers, clips, staples, pins, films, etc. Alternatively, they can be thermosetting materials formed by crosslinking reactions which lead to high-molecular-weight materials that do not melt or form flowable liquids at high temperatures.

Although thermoplastic and thermosetting biodegradable polymers have many useful biomedical applications, there are several important limitations to their use in the bodies of various animals including humans, animals, birds, fish, and reptiles. Because these polymers generally are

1 solids, all instances involving their use have required initially forming the
2 polymeric structures outside the body, followed by insertion of the solid
3 structure into the body. For example, sutures, clips, and staples are all
4 formed from thermoplastic biodegradable polymers prior to use. When
5 inserted into the body, they retain their original shape. While this
6 characteristic is essential for some uses, it is not preferred where it is desired
7 that the material be molded or flow to fill voids or cavities where it may be
8 most needed.

9 Drug delivery systems using thermoplastic or thermosetting
10 biodegradable polymers also often are or have to be formed outside the
11 body. In such instances, the drug is incorporated into the polymer and the
12 mixture is shaped into a certain form such as cylinder, disc, or fiber for
13 implantation. With such solid implants, the drug delivery system has to be
14 inserted into the body through an incision. These incisions are sometimes
15 larger than desired by the medical profession and occasionally lead to a
16 reluctance of the patient to accept such an implant or drug delivery system.
17 Nonetheless, both biodegradable and non-biodegradable implantable drug
18 delivery systems have been widely used successfully.

19 One reservoir device having a rate-controlling membrane and zero-
20 order release of an agent that is particularly designed for intraoral
21 implantation is described in U.S. Patent No. 5,085,866. The device is
22 prepared from a core that is sprayed with a solution having a polymer and a
23 solvent that is composed of a rapidly evaporating, low boiling point first
24 solvent and a slowly evaporating, high boiling point second solvent.

1 Other illustrative osmotic delivery systems include those disclosed in
2 U.S. Patent Nos. 3,797,492, 3,987,790, 4,008,719, 4,865,845, 5,057,318,
3 5,059,423, 5,112,614, 5,137,727, 5,151,093, 5,234,692, 5,234,693,
4 5,279,608, and 5,336,057. Pulsatile delivery devices are also known which
5 deliver a beneficial agent in a pulsatile manner as disclosed in U.S. Patent
6 Nos. 5,209,746, 5,308,348, and 5,456,679.

7 One way to avoid the incision needed to implant drug delivery systems
8 is to inject them as small particles, microspheres, or microcapsules. For
9 example, U.S. Patent No. 5,019,400 describes the preparation of controlled
10 release microspheres via a very low temperature casting process. These
11 materials may or may not contain a drug which can be released into the body.
12 Although these materials can be injected into the body with a syringe, they do
13 not always satisfy the demand for a biodegradable implant. Because they are
14 particulate in nature, they do not form a continuous film or solid implant with
15 the structural integrity needed for certain prostheses. When inserted into
16 certain body cavities such as a mouth, a periodontal pocket, the eye, or the
17 vagina where there is considerable fluid flow, these small particles,
18 microspheres, or microcapsules are poorly retained because of their small
19 size and discontinuous nature. Further, the particles tend to aggregate and
20 thus their behavior is hard to predict. In addition, microspheres or
21 microcapsules prepared from these polymers and containing drugs for
22 release into the body are sometimes difficult to produce on a large scale, and
23 their storage and injection characteristics present problems. Furthermore,
24 one other major limitation of the microcapsule or small-particle system is their

1 lack of reversibility without extensive surgical intervention. That is, if there
2 are complications after they have been injected, it is considerably more
3 difficult to remove them from the body than with solid implants. A still further
4 limitation on microparticles or microcapsulation is the difficulty in
5 encapsulating protein and DNA-based drugs without degradation caused by
6 denaturing solvents and temperature extremes used during processing.

7 The art has developed various drug delivery systems in response to
8 the aforementioned challenges. For instance, U.S. Patent No. 4,938,763 and
9 its divisional U.S. Patent No. 5,278,201 relate to a biodegradable polymer for
10 use in providing syringeable, in-situ forming, solid biodegradable implants for
11 animals. In one embodiment, a thermoplastic system is used wherein a non-
12 reactive polymer is dissolved in a water soluble biocompatible solvent to form
13 a liquid which is placed in the animal wherein the solvent dissipates to
14 produce the solid implant. Alternatively, a thermosetting system is used
15 wherein effective amounts of a liquid acrylic ester-terminated, biodegradable
16 prepolymer and a curing agent are formed and the liquid mixture is placed
17 within the animal wherein the prepolymer cures to form the solid implant. It is
18 stated that the systems provide a syringeable, solid biodegradable delivery
19 system by the addition of an effective level of a biologically active agent to the
20 liquid before the injection into the animal.

21 U.S. Patent 5,599,552 describes thermoplastic and thermoset polymer
22 compositions that utilize solvents which are miscible to dispersible in water,
23 such as N-methyl-2-pyrrolidone, resulting in polymer solutions capable of
24 quickly absorbing water from surrounding tissue. The polarity of the solvents

1 is described as being effective to provide about at least 10% solubility in
2 water. The polymer matrix systems are described as forming a porous core
3 surrounded by a porous skin.

4 U.S. Patent No. 5,242,910 describes a sustained release composition
5 containing drugs for treating periodontal disease. The composition comprises
6 copolymers of lactide and glycolide, triacetin (as a solvent/plasticizer) and an
7 agent providing relief of oral cavity diseases. The composition can take the
8 form of a gel and can be inserted into a periodontal cavity via a syringe using
9 either a needle or a catheter. As additional optional components, the
10 composition can contain surfactants, flavoring agents, viscosity controlling
11 agents, complexing agents, antioxidants, other polymers, gums, waxes/oils,
12 and coloring agents. One illustrative viscosity controlling agent set forth in
13 one of the examples is polyethylene glycol 400.

14 U.S. Patent No. 5,620,700 describes a polymer-drug matrix, optionally
15 including plasticizers in an amount up to about 30 wt %, for local application
16 of drug in the periodontal cavity. Among the plasticizers listed are, *inter alia*,
17 triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate,
18 diethyl phthalate, diethyl tartrate, ethyl lactate, triacetin and diacetin. The
19 polymer matrix is non-flowable prior to administration and is heated to
20 become flowable so that it may be dispensed into the periodontal cavity where
21 it solidifies. While the patent discusses possible systemic applications by
22 delivery via the ocular sacs of the eye or intravaginal delivery, it does not
23 address the issue of burst of drug or methods of controlling burst.

1 U.S. Patent No. 3,923,939 describes a method of reducing initial burst
2 of an active agent from a delivery device by removing, prior to implantation,
3 active agent from the exterior surface of the delivery device and through a
4 layer of at least 5% of the overall body thickness extending from the exterior
5 surface of the device.

6 U.S. Patent No. 5,556,905 describes degradable thermoplastic
7 compositions which are modified by plasticizers consisting of various partial
8 esters of citric acid.

9 Prior art polymer compositions for injectable implants have used
10 solvent/plasticizers that are very or relatively soluble in aqueous body fluids to
11 promote rapid solidification of the polymer at the implant site and promote
12 diffusion of drug from the implant. However, it has now been observed that a
13 serious problem associated with prior art polymeric implants utilizing water
14 soluble polymer solvents is the rapid migration of water into the polymer
15 composition when the implant is placed in the body and exposed to aqueous
16 body fluids. That characteristic often results in uncontrolled release of
17 beneficial agent that is manifested by an initial, rapid release of beneficial
18 agent from the polymer composition, corresponding to a "burst" of beneficial
19 agent being released from the implant. The burst often results in a
20 substantial portion of the beneficial agent, if not all, being released in a very
21 short time, e.g., hours or 1-2 days. Such an effect can be unacceptable,
22 particularly in those circumstances where sustained delivery is desired, i.e.,
23 delivery of beneficial agent over a period of a week or a month or more, or
24 where there is a narrow therapeutic window and release of excess beneficial

1 agent can result in adverse consequences to the subject being treated, or
2 where it is necessary to mimic the naturally-occurring daily profile of beneficial
3 agents, such as hormones and the like, in the body of the subject being
4 treated.

5 In an attempt to control burst and modulate and stabilize the delivery of
6 the beneficial agent the prior art has coated particles of beneficial agent to
7 retard release into an aqueous environment and extend release of the
8 beneficial agent over time. Alternatively, various stabilizing or release
9 modulating agents, such as metal salts as described in U.S. Patents
10 5,656,297; 5,654,010; 4,985,404 and 4,853,218 have been used.

11 Notwithstanding some success, those methods have not been entirely
12 satisfactory for the large number of beneficial agents that would be effectively
13 delivered by implants, since in many instances the modulation and
14 stabilization effect is the result of the formation of a complex of the metal ion
15 with the beneficial agent. When such complexes do not form, the
16 stabilization/modulation effect may not be adequate to prevent undesirable
17 "burst" of the beneficial agent upon its introduction into the implant site.

18 Additionally, with conventional low viscosity, solvent-based depot
19 compositions comprised of a polymer dissolved in a solvent, another problem
20 which often exists is that the composition solidifies slowly after injection as
21 solvent diffuses from the depot and water migrates into the depot. Since
22 these compositions are relatively non-viscous in order to be injected, a large
23 percentage of drug may be rapidly released as the system forms by diffusion
24 of the solvent, particularly when the beneficial agent is soluble in the solvent

1 and the solvent rapidly disperses into body fluids. Rapid solvent release
2 contributes to the "burst" effect along with depot hardening due to water
3 uptake. In this respect, it is typical for conventional solvent-based
4 compositions to have a drug burst wherein 30-75% of the drug contained in
5 the composition is released within one day of the initial injection.

6 The rapid water uptake into the polymer implant and solvent dispersion
7 into body fluids exhibited by prior art devices often results in implants having
8 pore structures that are non-homogeneous in size and shape. Typically, the
9 surface pores take on a finger-like pore structure extending for as much as
10 1/3 of a millimeter or more from the implant surface into the implant, and such
11 finger-like pores are open at the surface of the implant to the environment of
12 use. The internal pores tend to be smaller and less accessible to the fluids
13 present in the environment of use. Accordingly, when such devices are
14 implanted, the finger-like pores allow very rapid uptake of aqueous body
15 fluids into the interior of the implant with consequent immediate and rapid
16 dissolution of significant quantities of beneficial agent and unimpeded
17 diffusion of beneficial agent into the environment of use, producing the burst
18 effect discussed above.

19 Furthermore, rapid water uptake can result in premature polymer
20 precipitation such that a hardened implant or one with a hardened skin is
21 produced. The inner pores and much of the interior of the polymer containing
22 beneficial agent are shut off from contact with the body fluids and a significant
23 reduction in the release of beneficial agent can result over a not insignificant
24 period of time ("lag time"). That lag time is undesirable from the standpoint of

1 presenting a controlled, sustained release of beneficial agent to the subject
2 being treated. What one observes, then, is a burst of beneficial agent being
3 released in a short time period immediately after implantation, a lag time in
4 which no or very little beneficial agent is being released, and subsequently
5 continued delivery of beneficial agent (assuming beneficial agent remains
6 after the burst) until the supply of beneficial agent is exhausted.

7 SUMMARY OF THE INVENTION

8 The present invention provides a method and an implantable system
9 for systemic and local delivery of a beneficial agent to a subject. The method
10 and system provide controlled release of beneficial agent to the subject being
11 treated and limit the initial burst of beneficial agent from the implant system.
12 Additionally, the invention provides a method of preparing implant systems
13 having restricted initial burst of beneficial agent.

14 In one aspect, the invention comprises a method of administering,
15 locally or systemically, a beneficial agent to a subject which comprises
16 implanting a system comprising a beneficial agent dispersed or dissolved
17 substantially throughout a viscous gel, the system releasing 20% or less by
18 weight of the beneficial agent present in the viscous gel within the first 24
19 hours after implantation in the subject. Preferably, 10% or less by weight of
20 the beneficial agent will be released within the first 24 hours after
21 implantation.

22 In another aspect, the invention comprises a method of systemically
23 administering a beneficial agent to a subject which comprises implanting a

1 system comprising a beneficial agent dispersed or dissolved substantially
2 throughout a viscous gel, the system having a burst index of 8 or less.

3 In still another aspect, the invention comprises a method of
4 systemically administering a beneficial agent to a subject in a controlled
5 manner approximating zero order release by implanting a gel composition
6 comprising a biocompatible polymer, a biocompatible solvent having a
7 solubility in water of less than 7% and forming a viscous gel with the polymer,
8 and a beneficial agent, wherein the loading of the beneficial agent in the
9 interior of the polymer gel is above that required to saturate the beneficial
10 agent in water.

11 In still another aspect, the invention comprises an implantable,
12 biodegradable composition for the systemic delivery of a beneficial agent to a
13 subject wherein the composition comprises a polymer; an amount of a solvent
14 to form a viscous gel with the polymer, and a beneficial agent dissolved or
15 dispersed in the gel, wherein the solvent comprises a single solvent or a
16 mixture of solvents with at least one solvent having a miscibility in water of
17 less than 7% by weight and the amount of solvent constituting 40% or more
18 by weight of the gel vehicle.

19 In a further aspect, the present invention comprises an implantable,
20 biodegradable composition for the sustained delivery of a beneficial agent to
21 a subject wherein the composition comprises a polymer; an effective
22 plasticizing amount of a solvent to form a viscous gel with the polymer; and a
23 beneficial agent dissolved or dispersed in the gel, wherein the solvent
24 comprises a mixture of solvents with at least one solvent in the mixture

1 having a miscibility in water of less than 7% by weight. Preferably, the
2 miscibility in water of the solvent mixture is 20% or less by weight, and more
3 preferably 10% or less by weight.

4 In yet another aspect, the invention comprises an implantable,
5 biodegradable composition for delivery of a beneficial agent to a subject
6 wherein the composition comprises a polymer; an effective plasticizing
7 amount of a solvent to form a viscous gel with the polymer; and a beneficial
8 agent dissolved or dispersed in the gel, wherein the solvent comprises a
9 single solvent or a mixture of solvents with at least one solvent having a
10 miscibility in water of less than 7% by weight selected from lower alkyl and
11 aralkyl esters of benzoic acid.

12 In another aspect the present invention provides an implantable gel
13 composition for systemic delivery of a beneficial agent to a subject
14 comprising:

15 A) a biocompatible polymer;

16 B) a biocompatible solvent, having miscibility in water of less than
17 7% by weight and capable of dissolving the polymer and forming a viscous
18 gel, said solvent being selected from the group comprising compounds
19 having the following structural formula:

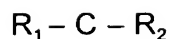


1 and

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4 wherein R_1 is lower alkyl, aryl or aralkyl and R_2 is aralkyl or lower alkyl; and R_1
5 and R_2 may be the same or different; with the proviso that when R_1 and R_2 are
6 each lower alkyl, the number of total carbon atoms represented by R_1 and R_2
7 combined is 4 or more;

8 C) a beneficial agent; and, optionally, one or more of the following:

9 D) an emulsifying agent;

10 E) a pore former;

11 F) a solubility modulator of the beneficial agent; and

12 G) an osmotic agent.

13

14 In another aspect the present invention provides an implantable gel
15 composition comprising:

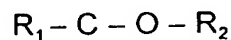
16 A) a biocompatible polymer;

17 B) a biocompatible solvent having miscibility in water of less than
18 7% by weight and capable of dissolving the polymer and forming a viscous
19 gel, said solvent being selected from the group comprising compounds
20 having the following structural formula:

21

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22



23 wherein R_1 and R_2 are as defined above.

1 In a further aspect, the present invention provides a method of
2 restricting uptake of water by a gel composition which comprises forming the
3 gel composition from a polymer and a solvent that forms a viscous gel with
4 the polymer, the solvent having a miscibility in water of less than 7% by
5 weight. Preferably, the solvent will have a miscibility in water of 6% or less by
6 weight, and more preferably 5% or less by weight.

7 In another aspect, the present invention provides a method of
8 preparing an injectable gel composition comprising:

9 A) mixing a biocompatible polymer and a solvent having a miscibility in
10 water of 7% or less selected from lower alkyl and aralkyl esters of benzoic
11 acid to form a viscous gel;

12 B) dispersing or dissolving a beneficial agent, optionally associated
13 with a solubility modulator of the beneficial agent, in an emulsifying agent to
14 form a beneficial agent containing emulsifying agent; and

15 C) mixing the beneficial agent containing emulsifying agent with the
16 viscous gel, said beneficial agent containing emulsifying agent forming a
17 dispersed droplet phase in the viscous gel, and optionally,

18 D) mixing one or more of a pore former and an osmotic agent with
19 said viscous gel.

20 In another aspect, the present invention provides a method of
21 preparing an implantable gel composition comprising:

22 A) mixing a biocompatible polymer and a solvent having a miscibility in
23 water of 7% or less selected from lower alkyl and aralkyl esters of
24 benzoic acid to form a viscous gel;

1 B) dispersing or dissolving a beneficial agent, optionally associated
2 with a solubility modulator of the beneficial agent, in the viscous
3 gel; and;

4 C) optionally mixing one or more of the following: an emulsifying
5 agent, a pore former, a solubility modulator of the beneficial agent
6 and an osmotic agent, with the beneficial agent containing gel.

7 In yet another aspect, the invention provides a gel composition
8 comprising:

9 A) a biocompatible polymer;

10 B) a biocompatible solvent having a miscibility in water of less than
11 7% by weight;

12 C) a beneficial agent selected from the group consisting of cDNA,
13 DNA, peptides, proteins and fragments and derivatives thereof, and
14 optionally, one or more of the following:

15 D) an emulsifying agent;

16 E) a pore former;

17 F) a solubility modulator of the beneficial agent; and

18 G) an osmotic agent;

19 wherein the composition has a burst index of less than 8.

20 In still another aspect, the invention comprises a kit for administration
21 of a beneficial agent to a subject comprising:

22 A) a biocompatible polymer;

23 B) a solvent having a miscibility in water of 7% or less by weight that is
24 suitable for dissolving the polymer and forming a viscous gel;

- 1 C) a beneficial agent; and optionally, one or more of the following:
- 2 D) an emulsifying agent;
- 3 E) a pore former;
- 4 F) a solubility modulator of the beneficial agent, optionally associated
- 5 with the beneficial agent; and
- 6 G) an osmotic agent;
- 7 wherein at least the beneficial agent, optionally associated with the solubility
- 8 modulator, is maintained separated from the solvent until the time of
- 9 administration of the beneficial agent to a subject.

10 In still another aspect, the invention comprises an implantable

11 composition for the systemic delivery of a beneficial agent comprising a

12 poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a

13 solvent to form a viscous gel with the polymer; and a beneficial agent

14 selected from the group consisting of cDNA, DNA, peptides, proteins and

15 fragments and derivatives thereof, said composition having a burst index of 8

16 or less.

17 In another aspect, the invention comprises an implantable composition

18 for the sustained delivery of a beneficial agent comprising a poly(lactide-co-

19 glycolide) copolymer; an effective plasticizing amount of a solvent selected

20 from lower alkyl and aralkyl esters of benzoic acid to form a viscous gel with

21 the polymer; and a beneficial agent.

22 In a further aspect, the invention comprises an implantable

23 composition comprising a viscous gel and a beneficial agent dispersed or

1 dissolved therein, wherein the viscous gel maintains a glass transition
2 temperature of less than 37°C for at least the first 24 hours after implantation.

3 In yet another aspect, the invention comprises a method of
4 administering a beneficial agent to a subject which comprises implanting a
5 system comprising a beneficial agent dissolved or dispersed substantially
6 throughout a viscous gel formed of a biocompatible polymer and a solvent
7 having a solubility in water of 7% or less, and a solubility modulator of the
8 beneficial agent, the system having a burst index of 8 or less.

9 In a further aspect, the invention comprises an implantable system
10 comprising a beneficial agent dissolved or dispersed substantially throughout
11 a viscous gel formed of a biocompatible polymer and a solvent having a
12 solubility in water of 7% or less, and a solubility modulator of the beneficial
13 agent, the system having a burst index of 8 or less.

14

15 BRIEF DESCRIPTION OF THE DRAWINGS

16 The foregoing and other objects, features and advantages of the
17 present invention will be more readily understood upon reading the following
18 detailed description in conjunction with the drawings in which:

19 Figure 1 is a graph illustrating the dispense force required to dispense
20 emulsified and non-emulsified viscous gel compositions through a 20 gauge
21 needle in psig at 2 cc/min;

22 Figure 2 is a graph illustrating the *in vitro* release profiles of lysozyme
23 from three different compositions in days;

1 Figure 3 is a graph illustrating the viscosity profiles of emulsions at
2 different shear rates of water alone and of an aqueous mixture of ethanol,
3 and of the viscous gel without emulsifying agent;

4 Figures 4A and 4B are graphs illustrating the degree of water uptake
5 for various polymer-solvent mixtures, some of which form a part of this
6 invention, and demonstrating that as the miscibility of the solvent in water
7 decreases, the amount of water taken up into the implant decreases; and

8 Figures 5A and 5B are graphs of *in vivo* release rate profiles of non-
9 stabilized and zinc-stabilized human growth hormone from gels formed from
10 PLGA and the solvents triacetin and benzyl benzoate, respectively.

11 DETAILED DESCRIPTION OF THE INVENTION

12 The present invention is directed to a method of systemically or locally
13 administering a beneficial agent to a subject by implanting in the subject an
14 implantable system, formed as a viscous gel from a biocompatible polymer
15 and a biocompatible solvent, and a beneficial agent is substantially dissolved
16 or dispersed throughout the gel. By appropriate choice of solvent, water
17 migration from the aqueous environment surrounding the implant system is
18 restricted, and beneficial agent is released to the subject over a prolonged
19 period of time, thus providing for delivery of the beneficial agent with a
20 controlled burst of beneficial agent and sustained release thereafter.

21 It has been discovered that when a solvent having a solubility in water
22 of less than 7% by weight in water is present in the system, suitable burst
23 control and sustained delivery of beneficial agent is achieved, whether or not
24 a solubility modulator of the beneficial agent is present in the system.

1 Typically, the implant systems useful in this invention will release, in the first
2 24 hours after implantation, 20% or less of the total amount of beneficial
3 agent to be delivered to the subject from the implant system, preferably 15%
4 or less and more preferably 10% or less. The viscous gel formed preferably
5 is bioerodible so that the implant system does not have to be surgically
6 removed after beneficial agent is depleted from the implant.

7 Water uptake and burst may be controlled by using polymer-solvent
8 compositions wherein the solvent is substantially immiscible in water, i.e., less
9 than 7% by weight soluble in water, so as to control the rate of water
10 migration into the polymer implant and ultimately control the burst of
11 beneficial agent and the sustained delivery of beneficial agent. Generally, the
12 compositions of the invention will be gel-like and will form with a substantially
13 homogeneous pore structure throughout the implant upon implantation and
14 during drug delivery, even as it hardens. Furthermore, while the polymer gel
15 implant will slowly harden when subjected to an aqueous environment, the
16 hardened implant may maintain a rubbery (non-rigid) composition with the
17 glass transition temperature being below 37°C.

18 Since the compositions often will be highly viscous prior to
19 implantation, when the composition is intended for implantation by injection,
20 the viscosity optionally may be modified by emulsifiers to obtain a gel
21 composition having a viscosity low enough to permit passage of the gel
22 composition through a needle. Also, pore formers and solubility modulators
23 of the beneficial agent may be added to the implant systems to provide
24 desired release profiles from the implant systems, along with typical

1 pharmaceutical excipients and other additives that do not change the
2 beneficial aspects of the present invention. The addition of a solubility
3 modulator to the implant system may enable the use of a solvent having a
4 solubility of 7% or greater in the implant system with minimal burst and
5 sustained delivery under particular circumstances. However, it is presently
6 preferred that the implant system utilize at least one solvent having a
7 solubility in water of less than 7% by weight, whether the solvent is present
8 alone or as part of a solvent mixture. It has also been discovered that when
9 mixtures of solvents which include a solvent having 7% or less by weight
10 solubility in water and one or more miscible solvents, optionally having
11 greater solubility, are used, implant systems exhibiting limited water uptake
12 and minimal burst and sustained delivery characteristics are obtained.

13 Definitions

14 The term "beneficial agent" means an agent that effects a desired
15 beneficial, often pharmacological, effect upon administration to a human or an
16 animal, whether alone or in combination with other pharmaceutical excipients
17 or inert ingredients.

18 The term "AUC" means the area under the curve obtained from an *in*
19 *vivo* assay in a subject by plotting blood plasma concentration of the
20 beneficial agent in the subject against time, as measured from the time of
21 implantation of the composition, to a time "*t*" after implantation. The time *t* will
22 correspond to the delivery period of beneficial agent to a subject.

23 The term "burst index" means, with respect to a particular composition
24 intended for systemic delivery of a beneficial agent, the quotient formed by

1 dividing (i) the AUC calculated for the first twenty-four hours after implantation
2 of the composition into a subject divided by the number 24, by (ii) the AUC
3 calculated for the time period of delivery of beneficial agent, divided by the
4 number of hours in the total duration of the delivery period.

5 The phrase "dissolved or dispersed" is intended to encompass all
6 means of establishing a presence of beneficial agent in the gel composition
7 and includes dissolution, dispersion, suspension and the like.

8 The term "systemic " means, with respect to delivery or administration
9 of a beneficial agent to a subject, that beneficial agent is detectable at a
10 biologically-significant level in the blood plasma of the subject.

11 The term "local " means, with respect to delivery or administration of a
12 beneficial agent to a subject, that beneficial agent is delivered to a localized
13 site in the subject but is not detectable at a biologically-significant level in the
14 blood plasma of the subject.

15 The term "gel vehicle" means the composition formed by mixture of the
16 polymer and solvent in the absence of the beneficial agent.

17 The term "prolonged period" means a period of time over which
18 release of a beneficial agent from the implant of the invention occurs, which
19 will generally be about one week or longer, and preferably about 30 days or
20 longer.

21 The term "initial burst" means, with respect to a particular composition
22 of this invention, the quotient obtained by dividing (i) the amount by weight of
23 beneficial agent released from the composition in a predetermined initial
24 period of time after implantation, by (ii) the total amount of beneficial agent

1 that is to be delivered from an implanted composition. It is understood that
2 the initial burst may vary depending on the shape and surface area of the
3 implant. Accordingly, the percentages and burst indices associated with
4 initial burst described herein are intended to apply to compositions tested in a
5 form resulting from dispensing of the composition from a standard syringe.

6 The term "solubility modulator" means, with respect to the beneficial
7 agent, an agent that will alter the solubility of the beneficial agent, with
8 reference to polymer solvent or water, from the solubility of beneficial agent in
9 the absence of the modulator. The modulator may enhance or retard the
10 solubility of the beneficial agent in the solvent or water. However, in the case
11 of beneficial agents that are highly water soluble, the solubility modulator will
12 generally be an agent that will retard the solubility of the beneficial agent in
13 water. The effects of solubility modulators of the beneficial agent may result
14 from intereactions of the solubility modulator with the solvent, or with the
15 beneficial agent itself, such as by the formation of complexes, or with both.
16 For the purposes hereof, when the solubility modulator is "associated" with
17 the beneficial agent, all such interactions or formations as may occur are
18 intended. Solubility modulators may be mixed with the beneficial agent prior
19 to its combination with the viscous gel or may be added to the viscous gel
20 prior to the addition of the beneficial agent, as appropriate.

21 The term "subject" means, with respect to the administration of a
22 composition of the invention, an animal or a human being.

23 Since all solvents, at least on a molecular level, will be soluble in water
24 (i.e., miscible with water) to some very limited extent, the term "immiscible" as

1 used herein means that 7% or less by weight of the solvent is soluble in or
2 miscible with water. For the purposes of this disclosure, solubility values of
3 solvent in water are considered to be determined at 20°C. Since it is
4 generally recognized that solubility values as reported may not always be
5 conducted at the same conditions, solubility limits recited herein as percent
6 by weight miscible or soluble with water as part of a range or upper limit may
7 not be absolute. For example, if the upper limit on solvent solubility in water
8 is recited herein as "7% by weight", and no further limitations on the solvent
9 are provided, the solvent "triacetin", which has a reported solubility in water of
10 7.17 grams in 100 ml of water, is considered to be included within the limit of
11 7%. A solubility limit in water of less than 7% by weight as used herein does
12 not include the solvent triacetin or solvents having solubilities in water equal
13 to or greater than triacetin.

14 The polymer, solvent and other agents of the invention must be
15 biocompatible; that is they must not cause irritation or necrosis in the
16 environment of use. The environment of use is a fluid environment and may
17 comprise a subcutaneous or intramuscular portion or body cavity of a human
18 or animal.

19 Polymers that may be useful in the invention may be biodegradable
20 and may include, but are not limited to polylactides, polyglycolides,
21 polycaprolactones, polyanhydrides, polyamines, polyurethanes,
22 polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals,
23 polycarbonates, polyorthocarbonates, polyphosphazenes, succinates,
24 poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol,

1 polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and
2 mixtures thereof.

3 Presently preferred polymers are polylactides, that is, a lactic acid-
4 based polymer that can be based solely on lactic acid or can be a copolymer
5 based on lactic acid and glycolic acid which may include small amounts of
6 other comonomers that do not substantially affect the advantageous results
7 which can be achieved in accordance with the present invention. As used
8 herein, the term "lactic acid" includes the isomers L-lactic acid, D-lactic acid,
9 DL-lactic acid and lactide while the term "glycolic acid" includes glycolide.
10 Most preferred are poly(lactide-co-glycolide)copolymers, commonly referred
11 to as PLGA. The polymer may have a monomer ratio of lactic acid/glycolic
12 acid of from about 100:0 to about 15:85, preferably from about 60:40 to about
13 75:25 and an especially useful copolymer has a monomer ratio of lactic
14 acid/glycolic acid of about 50:50.

15 The lactic acid-based polymer has a number average molecular weight
16 of from about 1,000 to about 120,000, preferably from about 5,000 to about
17 30,000 as determined by gas phase chromatography. As indicated in
18 aforementioned U.S. Patent No. 5,242,910, the polymer can be prepared in
19 accordance with the teachings of U.S. Patent No. 4,443,340. Alternatively,
20 the lactic acid-based polymer can be prepared directly from lactic acid or a
21 mixture of lactic acid and glycolic acid (with or without a further comonomer)
22 in accordance with the techniques set forth in U.S. Patent No. 5,310,865.
23 The contents of all of these patents are incorporated by reference. Suitable
24 lactic acid-based polymers are available commercially. For instance, 50:50

1 lactic acid:glycolic acid copolymers having molecular weights of 5,000,
2 10,000, 30,000 and 100,000, preferably about 8,000 to 13,000, and most
3 preferably about 10,000, and a wide variety of end groups to alter
4 susceptibility to hydrolysis and subsequent breakdown of the polymer chain
5 are available from Boehringer Ingelheim (Petersburg, VA).

6 The biocompatible polymer is present in the gel composition in an
7 amount ranging from about 5 to about 80% by weight, preferably from about
8 30 to about 70% by weight and often 40 to 60% by weight of the viscous gel,
9 the viscous gel comprising the combined amounts of the biocompatible
10 polymer and the solvent. The solvent will be added to polymer in amounts
11 described below, to provide implantable or injectable viscous gels.

12 The solvent must be biocompatible, should form a viscous gel with the
13 polymer, and restrict water uptake into the implant. The solvent may be a
14 single solvent or a mixture of solvents exhibiting the foregoing properties.
15 The term "solvent", unless specifically indicated otherwise, means a single
16 solvent or a mixture of solvents. Suitable solvents will substantially restrict
17 the uptake of water by the implant and may be characterized as immiscible in
18 water, i.e., having a solubility in water of less than 7% by weight. Preferably,
19 the solvents are five weight percent or less soluble in water; more preferably
20 three weight percent or less soluble in water; and even more preferably one
21 weight percent or less soluble in water. Most preferably the solubility of the
22 solvent in water is equal to or less than 0.5 weight percent.

23 Water miscibility may be determined experimentally as follows: Water
24 (1-5 g) is placed in a tared clear container at a controlled temperature, about

1 20°C, and weighed, and a candidate solvent is added dropwise. The solution
2 is swirled to observe phase separation. When the saturation point appears to
3 be reached, as determined by observation of phase separation, the solution
4 is allowed to stand overnight and is re-checked the following day. If the
5 solution is still saturated, as determined by observation of phase separation,
6 then the percent (w/w) of solvent added is determined. Otherwise more
7 solvent is added and the process repeated. Solubility or miscibility is
8 determined by dividing the total weight of solvent added by the final weight of
9 the solvent/water mixture. When solvent mixtures are used, for example 20%
10 triacetin and 80% benzyl benzoate, they are pre-mixed prior to adding to the
11 water.

12 Solvents useful in this invention are generally less than 7% water
13 soluble by weight as described above. Solvents having the above solubility
14 parameter may be selected from the lower alkyl and aralkyl esters of aryl
15 acids such as benzoic acid, the phthalic acids, salicylic acid, lower alkyl
16 esters of citric acid, such as triethyl citrate and tributyl citrate and the like, and
17 aryl, aralkyl and lower alkyl ketones. Among preferred solvents are those
18 having solubilities within the foregoing range selected from (i) compounds
19 having the following structural formulas :



1 and (i)



4 in which R_1 is aryl or aralkyl, R_2 is lower alkyl or aralkyl, and R_1 and R_2 are
5 optionally the same or different, with the proviso that when each of R_1 and R_2
6 are lower alkyl, the total carbon atoms in R_1 and R_2 combined are 4 or more,
7 and (ii) lower alkyl and aralkyl esters of phthalic acid, isophthalic acid and
8 terephthalic acid and (iii) lower alkyl and aralkyl esters of citric acid. For the
9 purposes hereof, lower alkyl means straight or branched chain hydrocarbons
10 having 1-6 carbon atoms, optionally substituted with non-interfering
11 substituents; aralkyl means (lower alkyl)phenyl, e.g., benzyl, phenethyl, 1-
12 phenylpropyl, 2-phenylpropyl, and the like wherein the alkyl moiety contains
13 from 1-6 carbon atoms; and aryl means phenyl, optionally substituted by non-
14 interfering substituents. Many of the solvents useful in the invention are
15 available commercially (Aldrich Chemicals, Sigma Chemicals) or may be
16 prepared by conventional esterification of the respective arylalkanoic acids
17 using acid halides, and optionally esterification catalysts, such as described in
18 US Patent No. 5,556,905, which is incorporated herein by reference, and in
19 the case of ketones, oxidation of their respective secondary alcohol
20 precursors.

21 Art recognized benzoic acid derivatives from which solvents having the
22 requisite solubility may be selected include: 1,4-cyclohexane dimethanol
23 dibenzoate, diethylene glycol dibenzoate, dipropylene glycol dibenzoate,

1 polypropylene glycol dibenzoate, propylene glycol dibenzoate, diethylene
2 glycol benzoate and dipropylene glycol benzoate blend, polyethylene glycol
3 (200) dibenzoate, iso decyl benzoate, neopentyl glycol dibenzoate, glyceryl
4 tribenzoate, pentaerythritol tetrabenzoate, cumylphenyl benzoate, trimethyl
5 pentanediol dibenzoate.

6 Art recognized phthalic acid derivatives from which solvents having the
7 requisite solubility may be selected include: Alkyl benzyl phthalate, bis-
8 cumyl-phenyl isophthalate, dibutoxyethyl phthalate, dimethyl phthalate,
9 dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diisobutyl phthalate,
10 butyl octyl phthalate, diisooheptyl phthalate, butyl octyl phthalate, diisonoyl
11 phthalate, nonyl undecyl phthalate, dioctyl phthalate, di-iso octyl phthalate,
12 dicapryl phthalate, mixed alcohol phthalate, di-(2-ethylhexyl) phthalate, linear
13 heptyl, nonyl, phthalate, linear heptyl, nonyl, undecyl phthalate, linear nonyl
14 phthalate, linear nonyl undecyl phthalate, linear dinoyl, didecyl phthalate
15 (diisodecyl phthalate), diundecyl phthalate, ditridecyl phthalate,
16 undecyldodecyl phthalate, decyltridecyl phthalate, blend (50/50) of dioctyl and
17 didecyl phthalates, butyl benzyl phthalate, and dicyclohexyl phthalate.

18 Preferred solvents include the lower alkyl and aralkyl esters of the aryl
19 acids described above. Representative acids are benzoic acid and the
20 phthalic acids, such as phthalic acid, isophthalic acid, and terephthalic acid.
21 Most preferred solvents are derivatives of benzoic acid and include, but are
22 not limited to, methyl benzoate, ethyl benzoate, n-propyl benzoate, isopropyl
23 benzoate, butyl benzoate, isobutyl benzoate, sec-butyl benzoate, tert-butyl

1 benzoate, isoamyl benzoate and benzyl benzoate, with benzyl benzoate
2 being most especially preferred. Preferred solvent mixtures are those in
3 which benzyl benzoate is the primary solvent, and mixtures formed of benzyl
4 benzoate and either triacetin, tributyl citrate, triethyl citrate or N-methyl-2-
5 pyrrolidone. Preferred mixtures are those in which benzyl benzoate is
6 present by weight in an amount of 50% or more, more preferably 60% or
7 more and most preferably 80% or more of the total amount of solvent present.
8 Especially preferred mixtures are those of 80/20 mixtures by weight of benzyl
9 benzoate/triacetin and benzyl benzoate/N-methyl-2-pyrrolidone.

10 It has been surprisingly found that the solvents described above
11 having a miscibility in water of less than 7% by weight may be mixed with one
12 or more additional miscible solvents ("component solvents"). Component
13 solvents compatible and miscible with the primary solvent may have a higher
14 miscibility with water and the resulting mixtures may still exhibit significant
15 restriction of water uptake into the implant. Such mixtures will be referred to
16 as "component solvent mixtures." Useful component solvent mixtures may
17 exhibit solubilities in water greater than the primary solvents themselves,
18 typically between 0.1 weight percent and up to and including 50 weight
19 percent, preferably up to and including 30 weight percent, and most
20 preferably up to an including 10 weight percent, without detrimentally
21 affecting the restriction of water uptake exhibited by the implants of the
22 invention. Especially preferred are component solvent mixtures having a
23 solubility in water of about 0.1% to about 7% by weight.

1 Component solvents useful in component solvent mixtures are those
2 solvents that are miscible with the primary solvent or solvent mixture, and
3 include, but are not limited, to triacetin, diacetin, tributyrin, triethyl citrate,
4 tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides,
5 triethyl phosphate, diethyl phthalate, diethyl tartrate, mineral oil, polybutene,
6 silicone fluid, glylcerin, ethylene glycol, polyethylene glycol, octanol, ethyl
7 lactate, propylene glycol, propylene carbonate, ethylene carbonate,
8 butyrolactone, ethylene oxide, propylene oxide, N-methyl-2-pyrrolidone, 2-
9 pyrrolidone, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl
10 ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam,
11 decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one, and
12 mixtures thereof.

13 In an especially preferred embodiment, the primary solvent is selected
14 from lower alkyl and aralkyl esters of benzoic acid and the polymer is a lactic-
15 acid based polymer, most preferably PLGA, having a number average
16 molecular weight of between about 8,000 to about 13,000, preferably about
17 10,000. Presently, the most preferred solvents are benzyl benzoate and the
18 lower alkyl esters of benzoic acid. The benzoic acid esters may be used
19 alone or in a mixture with other miscible solvents, e.g., triacetin, as described
20 herein. Implants are prepared as viscous gels in which the beneficial agent is
21 dissolved or dispersed substantially throughout, and such compositions are
22 useful both for systemic and local administration of beneficial agent, whether
23 or not initial burst is an important consideration. Additionally, use of esters of
24 benzoic acid provides increased control of water migration resulting in

1 increased stability of beneficial agent. The low water uptake, i.e., limited
2 water migration into the gel composition after implantation, permits the
3 practitioner of the invention to limit beneficial agent transfer by diffusion and
4 enhance control of the delivery profile of the beneficial agent by controlling
5 the bioerosion characteristics of the polymer. The preferred compositions
6 allow beneficial agent to be loaded into the interior of the polymer at levels
7 that are above that required to saturate the beneficial agent in water, thereby
8 facilitating zero order release of beneficial agent. Additionally, the preferred
9 compositions may provide viscous gels that have a glass transition
10 temperature that is less than 37°C, such that the gel remains non-rigid for a
11 period of time after implantation of 24 hours or more.

12 The solvent or solvent mixture is capable of dissolving the polymer to
13 form a viscous gel that can maintain particles of the beneficial agent
14 dissolved or dispersed and isolated from the environment of use prior to
15 release. The compositions of the present invention provide implants having a
16 low burst index. Water uptake is controlled by the use of a solvent or
17 component solvent mixture that solublizes or plasticizes the polymer but
18 substantially restricts uptake of water into implant.

19 The importance of restriction of water uptake can be appreciated by
20 reference to Figures 4A-4B illustrating bulk water uptake for various
21 compositions as a function of time and Table 1 illustrating representative
22 formulations for which burst indices have been determined.

23 Water uptake was determined for various polymer vehicles, i.e., 50%
24 polymer-50% solvent compositions, in the absence of beneficial agent. As

1 shown in Figure 4A, water uptake by a gel vehicle formed with the more water
2 miscible solvent N-methyl-2-pyrrolidone (NMP) is higher than that for any
3 other solvent-polymer combination, by about a factor of four or more. Water
4 uptake for the combination of 80% benzyl benzoate and 20% NMP by weight
5 in the solvent portion of the vehicle is less than a third that of NMP alone.
6 Implants with benzyl benzoate take up the least water, whether compared to
7 the other solvents alone or as mixtures with benzyl benzoate. Additionally, it
8 can be seen that the 80/20 mixture of benzyl benzoate and triacetin takes up
9 less than 10% water on a weight basis, and exhibits less water uptake than
10 triacetin alone. Figure 4B provides a comparison of various solvents alone
11 and demonstrates again the advantages of the benzoic acid esters,
12 particularly that of benzyl benzoate. A relative comparison of the water
13 uptake for the various solvents and the burst indices reproduced in the
14 foregoing Table 1 show a correlation between low water uptake values and
15 low burst indices. Gel compositions of this invention may take up 25 % or
16 less of their bulk weight in water within the first 7 days, 30% in the first 14
17 days and 40% in the first 21 days, as tested in the water migration assay
18 described herein.
19
20

Table 1

Solvent	Water Miscibility	Depot Gel ¹	Polymer ²	Zinc acetate (mM)	Process ³	Animal No.	Burst Index
Benzyl Benzoate	insol. in water (Merck)	D	PLGA-502	0	L	7 8	4.2 2.4
		K	PLGA-502	0	SD	21 22	3.6 2.4
		E	PLGA-502	7.5	L	9 10	4.5 2.3
		L	PLGA-502	7.5	SD	23 24	2.6 2.1
		F	PLGA-502	15	L	11 12	1.5 2.0
		F	PLGA-502	15	L	25 26	2.2 0.64
Triacetin	7% sol. in water (Merck)	A	PLGA-502	0	L	1 2	8.5 13
		I	PLGA-502	0	SD	17 18	12 10
		B	PLGA-502	7.5	L	3 4	4.1 2.1
		J	PLGA-502	7.5	SD	19 20	6.3 3.5
		C	PLGA-502	15	L	5 6	4.8 3.5
NMP	misc. with water (Merck)	G	PLGA-502	0	L	13 14	13 14
		H	PLGA-502	15	L	15 16	6.1 5.5

¹ All depot gels contained 10% hGH

² For all depot gels, hGH was loaded into (50/50) solvent / polymer vehicles

³ L = Lyophilized; SD = Spray-dried

In addition to the control of water uptake and associated initial burst by choice of solvent, agents that modulate the water solubility of the beneficial agent can also be utilized in conjunction with the preferred solvents to control burst of beneficial agent from the implant. Burst indices and percent of beneficial agent released in the first twenty-four

1 hours after implantation may be reduced by one-third to two-thirds or more by the use of
2 solubility modulators associated with the beneficial agent. Such modulators are typically
3 coatings, substances that form complexes or otherwise associate with or stabilize the
4 beneficial agent such as metallic ions, other stabilizing agents, waxes, lipids, oils, non-
5 polar emulsions, and the like. Use of such solubility modulators may permit the use of
6 more highly water soluble solvents or mixtures and achieve burst indices of 8 or less for
7 systemic applications, or with respect to local applications, release of beneficial agent in
8 the first 24 hours after implantation of not greater than 20% of the beneficial agent
9 administered. Preferably that release will be not greater than 15% and more preferably
10 not greater than 10%.

11 Limited water uptake by the compositions of this invention can often provide the
12 opportunity to prepare compositions without solubility modulators when in other
13 compositions such modulators would be necessary. For example with reference to
14 Table 1, suitable burst indices are obtained for a composition of PLGA, benzyl benzoate
15 and human growth hormone without the presence of Zn ion. Similar results may be
16 obtained with other beneficial agents, such as the interferons, including interferon alpha-
17 2a, interferon alpha-2b and consensus interferon.

18 In instances where the choice of solvent and polymer result in compositions
19 severely restricting water uptake by themselves, it may be desirable to add osmotic
20 agents or other agents and hydroattractants that facilitate water uptake to desired levels.
21 Such agents may be, for example, sugars and the like, and are well known in the art.

1 finger-like pores in the surface of implants formed using prior art processes.
2 Typically, a composition of the present invention takes the form of a
3 substantially, homogeneous, sponge-like gel, with the pores in the interior of
4 the implant being much the same as the pores on the surface of the implant.
5 Compositions of the present invention retain their gel-like consistency over a
6 longer period than do prior art devices and permit beneficial agent to be
7 delivered over a prolonged period. This is possible since the implants of the
8 present invention generally have a glass transition temperature, T_g , of less
9 than body temperature of the subject, e.g. 37°C for humans. Because of the
10 immiscibility of the solvents that are useful in this invention with water, water
11 uptake by the implant is restricted and the pores that do form tend to
12 resemble a closed cell structure without significant numbers of larger pores or
13 pores extending from the surface into the interior of the implant being open at
14 the surface of the implant. Furthermore, the surface pores offer only a limited
15 opportunity for water from body fluids to enter the implant immediately after
16 implantation, thus controlling the burst effect. Since the compositions often
17 will be highly viscous prior to implantation, when the composition is intended
18 for implantation by injection, the viscosity optionally may be modified by the
19 use of viscosity-reducing, miscible solvents or the use of emulsifiers, or by
20 heating to obtain a gel composition having a viscosity or shear resistance low
21 enough to permit passage of the gel composition through a needle.

22 The limit on the amount of beneficial agent released in the first 24
23 hours that is either desired or required will depend on circumstances such as
24 the overall duration of the delivery period, the therapeutic window for the

1 beneficial agent, potential adverse consequences due to overdosing, cost of
2 beneficial agent, and the type of effect desired, e.g., systemic or local.
3 Preferably, 20% or less of the beneficial agent will be released in the first 24
4 hours after implantation, where the percentage is based on the total amount
5 of beneficial agent to be delivered over the duration of the delivery period.
6 Typically, higher percentages of release in the first 24 hours can be tolerated
7 if the duration of the delivery period is relatively short, e.g., less than 7-14
8 days, or if the beneficial agent has a wide therapeutic window with little
9 likelihood of side effects, or if the beneficial agent acts locally.

10 Depending on the particular solvent or solvent mixture selected, the
11 polymer and beneficial agent, and optionally solubility modulators of the
12 beneficial agent, the compositions of the present invention intended for
13 systemic delivery may provide a gel composition having a burst index of 8 or
14 less, preferably 6 or less, more preferably 4 or less and most preferably 2 or
15 less. Compositions of PLGA with solvents having a miscibility in water of less
16 than 7% by weight, optionally combined with the other solvents, providing
17 implants intended for systemic delivery of beneficial agent having a burst
18 index of 10 or less, preferably 7 or less, more preferably 5 or less and most
19 preferably 3 or less, are particularly advantageous. The use of solvent
20 mixtures as discussed herein can be particularly advantageous as a means of
21 providing sufficient plasticizing of the polymer to obtain viscous gel formation
22 and at the same time meet the desired burst indices and percentage release
23 objectives of the compositions of the invention.

1 Compositions intended for local delivery of beneficial agent are formed
2 in the same manner as those intended for systemic use. However, because
3 local delivery of beneficial agent to a subject will not result in detectable
4 plasma levels of beneficial agent, such systems have to be characterized by
5 a percentage of beneficial agent released in a predetermined initial period,
6 rather than a burst index as defined herein. Most typically, that period will be
7 the first 24 hours after implantation and the percentage will be equal to the
8 amount by weight of the beneficial agent released in the period (e.g. 24
9 hours) divided by the amount by weight of the beneficial agent intended to be
10 delivered in the duration of the delivery period; multiplied by the number 100.
11 Compositions of the present invention will have initial bursts of 20% or less,
12 preferably 15% or less, most preferably 10% or less, for most applications.
13 Especially preferred are implant systems having initial bursts of 5% or less.

14 In many instances, it may be desirable to reduce the initial burst of
15 beneficial agent during local administration to prevent adverse effects. For
16 example, implants of the invention containing chemotherapeutic agents are
17 suitable for direct injection into tumors. However, many chemotherapeutic
18 agents may exhibit toxic side effects when administered systemically.
19 Consequently, local administration into the tumor may be the treatment
20 method of choice. It is necessary, however, to avoid administration of a large
21 burst of the chemotherapeutic agent if it is possible that such agent would
22 enter the vascular or lymphatic systems where it may exhibit side affects.
23 Accordingly, in such instances the implantable systems of the present
24 invention having limited burst as described herein are advantageous.

1 The solvent or solvent mixture is typically present in an amount of from
2 about 95 to about 20% by weight and is preferably present in an amount of
3 from about 70 to about 30% by weight and often 60-40% by weight of the
4 viscous gel, i.e., the combined amounts of the polymer and the solvent. The
5 viscous gel formed by mixing the polymer and the solvent typically exhibits a
6 viscosity of from about 1,000 to about 200,000 poise, preferably from about
7 5,000 to about 50,000 poise measured at a 1.0 sec^{-1} shear rate and 25°C
8 using a Haake Rheometer at about 1-2 days after mixing is completed.
9 Mixing the polymer with the solvent can be achieved with conventional low
10 shear equipment such as a Ross double planetary mixer for from about 10
11 minutes to about 1 hour, although shorter and longer periods may be chosen
12 by one skilled in the art depending on the particular physical characteristics of
13 the composition being prepared. Since it is often desirable to administer the
14 implant as an injectable composition, a countervailing consideration when
15 forming implants that are viscous gels is that the polymer/solvent/beneficial
16 agent composition have sufficiently low viscosity in order to permit it to be
17 forced through a small diameter, e.g., 18-20 gauge needle. If necessary,
18 adjustment of viscosity of the gel for injection can be accomplished with
19 emulsifying agents as described herein. Yet, such compositions should have
20 adequate dimensional stability so as to remain localized and be able to be
21 removed if necessary. The particular gel or gel-like compositions of the
22 present invention satisfy such requirements.

23 If the polymer composition is to be administered as an injectable gel,
24 the level of polymer dissolution will need to be balanced with the resulting gel

1 viscosity, to permit a reasonable force to dispense the viscous gel from a
2 needle, and the potential burst effect. Highly viscous gels enable the
3 beneficial agent to be delivered without exhibiting a significant burst effect,
4 but may make it difficult to dispense the gel through a needle. In those
5 instances, an emulsifying agent may optionally be added to the composition.
6 Also, since the viscosity may generally be lowered as the temperature of the
7 composition increases, it may be advantageous in certain applications to
8 reduce the viscosity of the gel by heating to provide a more readily injectable
9 composition.

10 For instance, as shown in Figure 1, a gel prepared from 40% by weight
11 of a 50:50 lactic acid:glycolic polymer and 60% by weight of triacetin required
12 about 40 psig to dispense the gel through a standard 20 gauge needle at 2
13 cc/min while a gel prepared from the same amount of polymer with 60% by
14 weight of N-methyl-2-pyrrolidone required only about 8 psig. Figure 1 further
15 shows that when the emulsifying agent (in this case 33% by weight of a 10%
16 ethanol solution) is added to the viscous gel according to the invention, the
17 dispense force needed is only about 2 psig. The shear thinning
18 characteristics of the depot gel compositions of the present invention allow
19 them to be readily injected into an animal including humans using standard
20 gauge needles without requiring undue dispensing pressure.

21 When the emulsifying agent is mixed with the viscous gel formed from
22 the polymer and the solvent using conventional static or mechanical mixing
23 devices, such as an orifice mixer, the emulsifying agent forms a separate
24 phase composed of dispersed droplets of microscopic size that typically have

1 an average diameter of less than about 100 microns. The continuous phase
2 is formed of the polymer and the solvent. The particles of the beneficial agent
3 may be dissolved or dispersed in either the continuous phase or the droplet
4 phase. In the resulting thixotropic composition, the droplets of emulsifying
5 agent elongate in the direction of shear and substantially decrease the
6 viscosity of the viscous gel formed from the polymer and the solvent. For
7 instance, with a viscous gel having a viscosity of from about 5,000 to about
8 50,000 poise measured at 1.0 sec^{-1} at 25°C , one can obtain a reduction in
9 viscosity to less than 100 poise when emulsified with a 10% ethanol/water
10 solution at 25°C as determined by Haake Rheometer.

11 When used, the emulsifying agent typically is present in an amount
12 ranging from about 5 to about 80%, preferably from about 20 to about 60%
13 and often 30 to 50% by weight based on the amount of the injectable depot
14 gel composition, that is the combined amounts of polymer, solvent,
15 emulsifying agent and beneficial agent. Emulsifying agents include, for
16 example, solvents that are not fully miscible with the polymer solvent or
17 solvent mixture. Illustrative emulsifying agents are water, alcohols, polyols,
18 esters, carboxylic acids, ketones, aldehydes and mixtures thereof. Preferred
19 emulsifying agents are alcohols, propylene glycol, ethylene glycol, glycerol,
20 water, and solutions and mixtures thereof. Especially preferred are water,
21 ethanol, and isopropyl alcohol and solutions and mixtures thereof. The type
22 of emulsifying agent affects the size of the dispersed droplets. For instance,
23 ethanol will provide droplets that have average diameters that can be on the

1 order of ten times larger than the droplets obtained with an isotonic saline
2 solution containing 0.9% by weight of sodium chloride at 21°C.

3 Figure 3 shows the viscosities at different shear rates using water
4 alone and an aqueous mixture containing 10% by volume of ethanol at a
5 weight ratio of 2:1 (gel:emulsifying agent) using a viscous gel formed from
6 50% by weight of a 50:50 lactic acid:glycolic acid copolymer and 50% by
7 weight of triacetin compared to the viscosities of the viscous gel without
8 emulsifying agent.

9 It is to be understood that the emulsifying agent does not constitute a
10 mere diluent that reduces viscosity by simply decreasing the concentration of
11 the components of the composition. The use of conventional diluents can
12 reduce viscosity, but can also cause the burst effect mentioned previously
13 when the diluted composition is injected. In contrast, the injectable depot
14 composition of the present invention can be formulated to avoid the burst
15 effect by selecting the solvent and emulsifying agent so that once injected
16 into place, the emulsifying agent has little impact on the release properties of
17 the original system.

18 Since the implant systems of the present invention preferably are
19 formed as viscous gels, the means of administration of the implants is not
20 limited to injection, although that mode of delivery may often be preferred.
21 Where the implant will be administered as a leave-behind product, it may be
22 formed to fit into a body cavity existing after completion of surgery or it may
23 be applied as a flowable gel by brushing or palleting the gel onto residual

1 tissue or bone. Such applications may permit loading of beneficial agent in
2 the gel above concentrations typically present with injectable compositions.

3 The beneficial agent can be any physiologically or pharmacologically
4 active substance or substances optionally in combination with
5 pharmaceutically acceptable carriers and additional ingredients such as
6 antioxidants, stabilizing agents, permeation enhancers, etc. that do not
7 substantially adversely affect the advantageous results that can be attained
8 by the present invention. The beneficial agent may be any of the agents
9 which are known to be delivered to the body of a human or an animal and
10 that are preferentially soluble in water rather than in the polymer-dissolving
11 solvent. These agents include drug agents, medicaments, vitamins,
12 nutrients, or the like. Included among the types of agents which meet this
13 description are lower molecular weight compounds, proteins, peptides,
14 genetic material, nutrients, vitamins, food supplements, sex sterilants, fertility
15 inhibitors and fertility promoters.

16 Drug agents which may be delivered by the present invention include
17 drugs which act on the peripheral nerves, adrenergic receptors, cholinergic
18 receptors, the skeletal muscles, the cardiovascular system, smooth muscles,
19 the blood circulatory system, synaptic sites, neuroeffector junctional sites,
20 endocrine and hormone systems, the immunological system, the reproductive
21 system, the skeletal system, autacoid systems, the alimentary and excretory
22 systems, the histamine system and the central nervous system. Suitable
23 agents may be selected from, for example, proteins, enzymes, hormones,
24 polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins,

1 polypeptides, steroids, analgesics, local anesthetics, antibiotic agents, anti-
2 inflammatory corticosteroids, ocular drugs and synthetic analogs of these
3 species.

4 Examples of drugs which may be delivered by the composition of the
5 present invention include, but are not limited to prochlorperzine edisylate,
6 ferrous sulfate, aminocaproic acid, mecamylamine hydrochloride,
7 procainamide hydrochloride, amphetamine sulfate, methamphetamine
8 hydrochloride, benzamphetamine hydrochloride, isoproterenol sulfate,
9 phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride,
10 pilocarpine hydrochloride, atropine sulfate, scopolamine bromide,
11 isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride,
12 methylphenidate hydrochloride, theophylline choline, cephalixin
13 hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate,
14 phenoxybenzamine, thiethylperzine maleate, anisindone, diphenadione
15 erythrityl tetranitrate, digoxin, isofluorophate, acetazolamide, methazolamide,
16 bendroflumethiazide, chloropromazine, tolazamide, chlormadinone acetate,
17 phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl
18 sulfisoxazole, erythromycin, hydrocortisone, hydrocorticosterone acetate,
19 cortisone acetate, dexamethasone and its derivatives such as
20 betamethasone, triamcinolone, methyltestosterone, 17-S-estradiol, ethinyl
21 estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17 α -
22 hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel,
23 norethindrone, norethisterone, norethindrone, progesterone, norgesterone,
24 norethynodrel, aspirin, indomethacin, naproxen, fenoprofen, sulindac,

1 indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol,
2 alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine,
3 methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate,
4 ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac,
5 ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem,
6 milrinone, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen,
7 fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal,
8 nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine,
9 tiapamil, gallopamil, amlodipine, mioflazine, lisinopril, enalapril, enalaprilat,
10 captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine, tetratolol,
11 minoxidil, chlordiazepoxide, diazepam, amitriptyline, and imipramine. Further
12 examples are proteins and peptides which include, but are not limited to,
13 bone morphogenic proteins, insulin, colchicine, glucagon, thyroid stimulating
14 hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin,
15 corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic
16 gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine
17 somatotropin, oxytocin, vasopressin, GRF, somatostatin, lypressin,
18 pancreozymin, luteinizing hormone, LHRH, LHRH agonists and antagonists,
19 leuprolide, interferons such as interferon alpha-2a, interferon alpha-2b, and
20 consensus interferon, interleukins, growth hormones such as human growth
21 hormone and its derivatives such as methione-human growth hormone and
22 des-phenylalanine human growth hormone, bovine growth hormone and
23 porcine growth hormone, fertility inhibitors such as the prostaglandins, fertility
24 promoters, growth factors such as insulin-like growth factor, coagulation

1 factors, human pancreas hormone releasing factor, analogs and derivatives
2 of these compounds, and pharmaceutically acceptable salts of these
3 compounds, or their analogs or derivatives.

4 The present invention also finds application with chemotherapeutic
5 agents for the local application of such agents to avoid or minimize systemic
6 side effects. Gels of the present invention containing chemotherapeutic
7 agents may be injected directly into the tumor tissue for sustained delivery of
8 the chemotherapeutic agent over time. In some cases, particularly after
9 resection of the tumor, the gel may be implanted directly into the resulting
10 cavity or may be applied to the remaining tissue as a coating. In cases in
11 which the gel is implanted after surgery, it is possible to utilize gels having
12 higher viscosities since they do not have to pass through a small diameter
13 needle. Representative chemotherapeutic agents that may be delivered in
14 accordance with the practice of the present invention include, for example,
15 carboplatin, cisplatin, paclitaxel, BCNU, vincristine, camptothecin, etoposide,
16 cytokines, ribozymes, interferons, oligonucleotides and oligonucleotide
17 sequences that inhibit translation or transcription of tumor genes, functional
18 derivatives of the foregoing, and generally known chemotherapeutic agents
19 such as those described in U.S. Patent 5,651,986. The present application
20 has particular utility in the sustained delivery of water soluble
21 chemotherapeutic agents, such as for example cisplatin and carboplatin and
22 the water soluble derivatives of paclitaxel. Those characteristics of the
23 invention that minimize the burst effect are particularly advantageous in the
24 administration of water soluble beneficial agents of all kinds, but particularly

1 those compounds that are clinically useful and effective but may have
2 adverse side effects.

3 To the extent not mentioned above, the beneficial agents described in
4 aforementioned U.S. Patent No. 5,242,910 can also be used. One particular
5 advantage of the present invention is that materials, such as proteins, as
6 exemplified by the enzyme lysozyme, and cDNA, and DNA incorporated into
7 vectors both viral and nonviral, which are difficult to microencapsulate or
8 process into microspheres can be incorporated into the compositions of the
9 present invention without the level of degradation caused by exposure to high
10 temperatures and denaturing solvents often present in other processing
11 techniques.

12 The beneficial agent is preferably incorporated into the viscous gel
13 formed from the polymer and the solvent in the form of particles typically
14 having an average particle size of from about 0.1 to about 100 microns,
15 preferably from about 1 to about 25 microns and often from 2 to 10 microns.
16 For instance, particles having an average particle size of about 5 microns
17 have been produced by spray drying or freeze drying an aqueous mixture
18 containing 50% sucrose and 50% chicken lysozyme (on a dry weight basis)
19 and mixtures of 10-20% hGH and 15-30 mM zinc acetate. Such particles
20 have been used in certain of the examples illustrated in the figures.
21 Conventional lyophilization processes can also be utilized to form particles of
22 beneficial agents of varying sizes using appropriate freezing and drying
23 cycles.

1 To form a suspension or dispersion of particles of the beneficial agent
2 in the viscous gel formed from the polymer and the solvent, any conventional
3 low shear device can be used such as a Ross double planetary mixer at
4 ambient conditions. In this manner, efficient distribution of the beneficial
5 agent can be achieved substantially without degrading the beneficial agent.

6 The beneficial agent is typically dissolved or dispersed in the
7 composition in an amount of from about 1 to about 50% by weight, preferably
8 in an amount of from about 5 to about 30% and often 10 to 20% by weight of
9 the combined amounts of the polymer, solvent and beneficial agent.
10 Depending on the amount of beneficial agent present in the composition, one
11 can obtain different release profiles and burst indices. More specifically, for a
12 given polymer and solvent, by adjusting the amounts of these components
13 and the amount of the beneficial agent, one can obtain a release profile that
14 depends more on the degradation of the polymer than the diffusion of the
15 beneficial agent from the composition or vice versa. In this respect, at lower
16 beneficial agent loading rates, one generally obtains a release profile
17 reflecting degradation of the polymer wherein the release rate increases with
18 time. At higher loading rates, one generally obtains a release profile caused
19 by diffusion of the beneficial agent wherein the release rate decreases with
20 time. At intermediate loading rates, one obtains combined release profiles so
21 that if desired, a substantially constant release rate can be attained. In order
22 to minimize burst, loading of beneficial agent on the order of 30% or less by
23 weight of the overall gel composition, i.e., polymer, solvent and beneficial
24 agent, is preferred, and loading of 20% or less is more preferred.

1 Release rates and loading of beneficial agent will be adjusted to
2 provide for therapeutically-effective delivery of the beneficial agent over the
3 intended sustained delivery period. Preferably, the beneficial agent will be
4 present in the polymer gel at concentrations that are above the saturation
5 concentration of beneficial agent in water to provide a drug reservoir from
6 which the beneficial agent is dispensed. While the release rate of beneficial
7 agent depends on the particular circumstances, such as the beneficial agent
8 to be administered, release rates on the order of from about 0.1 to about 100
9 micrograms/day, preferably from about 1 to about 10 micrograms per day, for
10 periods of from about 7 to about 90 days can be obtained. Greater amounts
11 may be delivered if delivery is to occur over shorter periods. Generally,
12 higher release rate is possible if a greater burst can be tolerated. In
13 instances where the gel composition is surgically implanted, or used as a
14 "leave behind" depot when surgery to treat the disease state or another
15 condition is concurrently conducted, it is possible to provide higher doses that
16 would normally be administered if the implant was injected. Further, the dose
17 of beneficial agent may be controlled by adjusting the volume of the gel
18 implanted or the injectable gel injected. As can be seen from Figure 2 with
19 respect to lysozyme, with more highly viscous systems, one can avoid a burst
20 effect and deliver on the order of 1% by weight of the beneficial agent in the
21 composition during the first day.

22 Figures 5A and 5B illustrate representative release profiles of human
23 growth hormone ("hGH") obtained in rats from preferred compositions of this
24 invention. The benefits of benzyl benzoate are apparent in that comparison.

1 The hGH-benzyl benzoate implant shows a lower burst and a nearly zero
2 order sustained release of hGH over the release period for both the case
3 wherein the hGH is not stabilized (Figure 5A) and the case in which hGH is
4 stabilized with zinc ions (Figure 5B).

5 Other components may be present in the gel composition, to the extent
6 they are desired or provide useful properties to the composition, such as
7 polyethylene glycol, hydroscopic agents, stabilizing agents, pore forming
8 agents, and others. When the composition includes a peptide or a protein
9 that is soluble in or unstable in an aqueous environment, it may be highly
10 desirable to include a solubility modulator, that may, for example, be a
11 stabilizing agent, in the composition. Various modulating agents are
12 described in U.S. Patent Nos. 5,654,010 and 5,656,297 which are
13 incorporated herein by reference. In the case of hGH, for example, it is
14 preferable to include an amount of a salt of a divalent metal, preferably zinc.
15 Examples of such modulators and stabilizing agents, which may form
16 complexes with the beneficial agent or associate to provide the stabilizing or
17 modulated release effect, include metal cations, preferably divalent, present
18 in the composition as magnesium carbonate, zinc carbonate, calcium
19 carbonate, magnesium acetate, magnesium sulfate, zinc acetate, zinc sulfate,
20 zinc chloride, magnesium chloride, magnesium oxide, magnesium hydroxide,
21 other antacids, and the like. The amounts of such agents used will depend
22 on the nature of the complex formed, if any, or the nature of the association
23 between the beneficial agent and the agent. Molar ratios of solubility

1 modulator or stabilizing agent to beneficial agent of about 100:1 to 1:1,
2 preferably 10:1 to 1:1, typically can be utilized.

3 Pore forming agents include, biocompatible materials that when
4 contacted with body fluids dissolve, disperse or degrade to create pores or
5 channels in the polymer matrix. Typically, organic and non-organic materials
6 that are water soluble such as sugars (e.g., sucrose, dextrose), water soluble
7 salts (e.g., sodium chloride, sodium phosphate, potassium chloride, and
8 sodium carbonate), water soluble solvents such as N-methyl-2-pyrrolidone
9 and polyethylene glycol and water soluble polymers (e.g.,
10 carboxymethylcellulose, hydroxypropylcellulose, and the like) can conveniently
11 be used as pore formers. Such materials may be present in amounts varying
12 from about 0.1% to about 100% of the weight of the polymer, but will typically
13 be less than 50% and more typically less than 10-20% of the weight of
14 polymer.

15 Compositions of this invention without beneficial agent are useful for
16 wound healing, bone repair and other structural support purposes.

17 To further understand the various aspects of the present invention, the
18 results set forth in the previously described Figures were obtained in
19 accordance with the following examples.

20 Example 1

21 Lysozyme particles were made by spray drying 50% sucrose and 50%
22 chicken lysozyme (on a dry weight basis).

23 A viscous gel material was prepared by heating 60% by weight of
24 triacetin with 40% by weight of a 50:50 lactic acid:glycolic acid copolymer to

1 37°C overnight. The viscous gel was allowed to cool to room temperature.
2 The lysozyme particles were added to the viscous gel in a ratio of 20:80
3 lysozyme particles:gel (by weight). The combination was mixed for 5
4 minutes. Immediately prior to use, a 10% ethanol, 90% isotonic saline
5 solution was added as the emulsifying agent. The emulsifying agent
6 comprised 1/3 of the total injectable depot gel composition. The prepared
7 compositions were suitable for injection.

8 Figure 2 shows the in vitro release rates obtained from the
9 compositions described with regard to Figure 1. The gel prepared from 40%
10 by weight of a 50:50 lactic acid:glycolic polymer and 60% by weight triacetin
11 is thick and thus difficult to inject but shows little burst (less than 2% of the
12 beneficial agent is delivered in the first eight days). The gel prepared from
13 40% by weight of a 50:50 lactic acid:glycolic polymer and 60% by weight n-
14 methyl-2-pyrrolidone is thin and injectable but shows a large burst (greater
15 than 70% of the beneficial agent is delivered in the first eight days). The gel
16 prepared from 27% by weight of a 50:50 lactic acid:glycolic polymer, 40% by
17 weight triacetin and 33% by weight of a 10% ethanol, 90% isotonic saline
18 solution is thin and injectable and shows little burst (less than 10% of the
19 beneficial agent is delivered in the first eight days). In each case, lysozyme is
20 the beneficial agent and comprises 20% by weight of the combined beneficial
21 agent, polymer and solvent formulation.

22 Example 2 - hGH Particle Preparation

23 Human growth hormone (hGH) particles (optionally containing zinc
24 acetate) were prepared as follows:

hGH solution (5 mg/ml) solution in water (BresaGen Corporation, Adelaide, Australia) was concentrated to 10 mg/mL using a Concentration/Dialysis Selector diafiltering apparatus. The diafiltered hGH solution was then washed with 5 times volume of tris or phosphate buffer solution (pH 7.6). Particles of hGH were then formed by spray drying or lyophilization using conventional techniques. Phosphate buffer solutions (5 or 50 mM) containing hGH (5 mg/mL) and various levels of zinc acetate (0 to 30 mM) were spray-dried using a Yamato Mini Spraydryer set at the following parameters:

Spray Dryer Parameter	Setting
Atomizing Air	2 psi
Inlet Temperature	120°C
Aspirator Dial	7.5
Solution Pump	2-4
Main Air Valve	40-45 psi

hGH particles having a size range between 2 - 100 microns were obtained. Lyophilized particles were prepared from tris buffer solutions (5 or 50 mM: pH 7.6) containing hGH (5 mg/mL) and various levels of zinc acetate (0 to 30 mM) using a Durastop μ P Lyophilizer in accordance with the following freezing and drying cycles:

Freezing Cycle	Ramp down at 2.5 C/min to -30 C and hold for 30 minutes
	Ramp down at 2.5 C/min from -30 C to -50C and hold for 60 minutes
Drying Cycle	Ramp up at 0.5 C/min to 10 C and hold for 960 min
	Ramp up at 0.5 C/min to 20 C and hold for 480 min
	Ramp up at 0.5 C/min to 25 C and hold for 300 min
	Ramp up at 0.5 C/min to 30 C and hold for 300 min
	Ramp down at 0.5 C/min to 5 C and hold for 5000 min

hGH particles having a size range between 2 - 100 microns were obtained.

1 hGH Zinc Complexed Solution Preparation

2 Zinc acetate solutions were prepared with tris buffer and phosphate
3 buffer. Desired molar volumes of trizma hydrochloride and trizma base were
4 prepared separately
5 (5 or 50 mM). The pH of trizma base solution was measured, and the
6 corresponding trizma hydrochloride solution was added to adjust the pH of
7 the trizma base solution, resulting with a final pH of 7.6. The desired molar
8 volume of zinc acetate was added to the buffer solution. Desired molar
9 volumes of sodium phosphate monobasic and sodium phosphate dibasic
10 were prepared separately (5 or 50 mM). Sodium azide (0.2% w/w) was
11 added to each phosphate solution. The pH of the dibasic solution was
12 measured, and the corresponding monobasic solution was added to adjust
13 the pH of the dibasic solution, resulting with a final pH of 7.6. The desired
14 molar volume of zinc acetate was added to the buffer solution. Tris or
15 phosphate buffer containing zinc acetate was added to the diafiltered hGH
16 solution to achieve the final desired zinc acetate molar volume (between 5
17 and 30 mM). The final hGH concentration was 5 mg/mL.

18 Gel Vehicle Preparation

19 A glass vessel was tared on a Mettler PJ3000 top loader balance. Poly
20 (D,L-lactide-co-glycolide) 50:50 RESOMER® RG502 (PLGA-502) was weighed
21 into the glass vessel. The glass vessel containing PLGA-502 was tared and
22 the corresponding solvent was added. Amounts expressed as percentages for
23 various polymer/solvent combinations are set forth in Table 2 below. The
24 polymer/solvent mixture was manually stirred with a stainless steel square-tip

1 spatula, resulting in a sticky amber paste-like substance containing white
2 polymer particles. The vessel containing the polymer/solvent mixture was
3 sealed and placed in a temperature controlled incubator equilibrated to 39°C.
4 The polymer/solvent mixture was removed from the incubator when it appeared
5 to be a clear amber homogeneous gel. Incubation time intervals ranged from 1
6 to 4 days, depending on solvent and polymer type and solvent and polymer
7 ratios. Additional depot gel vehicles are prepared with the following polymers:
8 Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® L104, PLGA-L104, code no.
9 33007, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG206, PLGA-206,
10 code no. 8815, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG502,
11 PLGA-502, code 0000366, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER®
12 RG502H, PLGA-502H, code no. 260187, Poly (D,L-lactide-co-glycolide) 50:50
13 RESOMER® RG503, PLGA-503, code no. 0080765, Poly (D,L-lactide-co-
14 glycolide) 50:50 RESOMER® RG506, PLGA-506, code no. 95051, Poly (D,L-
15 lactide-co-glycolide) 50:50 RESOMER® RG755, PLGA-755, code no. 95037,
16 (Boehringer Ingelheim Chemicals, Inc., Petersburg, VA), and the following
17 solvents or mixtures: glyceryl triacetate (Eastman Chemical Co., Kingsport,
18 TN), benzyl benzoate ("BB"), ethyl benzoate ("EB"), methyl benzoate ("MB"),
19 triacetin ("TA"), and triethyl citrate ("TC") (Aldrich Chemical Co., St Louis, MO).
20 When solvent combinations were used, for example 20% triacetin and 80%
21 benzyl benzoate, the solvent mixture was directly added to the pre-weighed dry
22 polymer. Typical polymer molecular weights were in the range of 14,400 -
23 39,700 (M_w) [6,400-12,200 (M_n)]. Representative gel vehicles are described in
24 Table 2 below.

Table 2: Gel Vehicles

Solvent/ Polymer	Solvent	Polymer	Amount Solvent	Amount Polymer	Gel Weight	Ratio
50/50	BB	PLGA-502	5 g	5 g	10 g	1.0
50/50	TA / BB Mixture	PLGA-502	5 g	5 g	10 g	1.0
60/40	TA / BB Mixture	PLGA-502	6 g	4 g	10 g	1.5
70/30	TA / BB Mixture	PLGA-502	7 g	3 g	10 g	2.3
80/20	TA / BB Mixture	PLGA-502	8 g	2 g	10 g	4.0
50/50	EB	PLGA-502	5 g	5 g	10 g	1.0
50/50	TA / EB Mixture	PLGA-502	5 g	5 g	10 g	1.0
50/50	BB	PLGA-502	25 g	25 g	50 g	1.0
55/45	BB	PLGA-502	27.5 g	22.5 g	50 g	1.2
50/50	BB	PLGA-502	50 g	50 g	100 g	1.0
50/50	TA / BB Mixture	PLGA-502	50 g	50 g	100 g	1.0
50/50	BB	PLGA-502H	5 g	5 g	10 g	1.0
50/50	BB	PLGA-503	50 g	50 g	100 g	1.0

Drug Loading

Spray-dried or lyophilized hGH particles (10 - 20% w/w), with and without zinc acetate, prepared as above were added to a specified clear amber depot gel vehicle and blended manually until the dry powder was wetted completely. Then, the milky light yellow particle/gel mixture was thoroughly blended by conventional mixing using a Caframo mechanical stirrer with an attached square-tip metal spatula. Resulting formulations are illustrated in Tables 3 and 4 below. "L" identifies lyophilized hGH particles and "SD" identifies spray dried hGH particles. Final homogenous gel formulations were transferred to 3, 10 or 30 cc disposable syringes for storage or dispensing.

Table 3: In Vivo hGH

Formulation	Polymer		Solvent		Drug Particle			Trizma Buffer (mM)
	Level	PLGA	Level	Type	Level	Process	Zinc Level (mM)	
A	45%	502	45%	TA	10%	L	0	50
B	45%	502	45%	TA	10%	L	7.5	50
C	45%	502	45%	TA	10%	L	15	50
D	45%	502	45%	BB	10%	L	0	50
E	45%	502	45%	BB	10%	L	7.5	50
F	45%	502	45%	BB	10%	L	15	50
G	45%	502	45%	NMP	10%	L	0	50
H	45%	502	45%	NMP	10%	L	15	50
I	45%	502	45%	TA	10%	SD	0	50
J	45%	502	45%	TA	10%	SD	7.5	50
K	45%	502	45%	BB	10%	SD	0	50
L	45%	502	45%	BB	10%	SD	7.5	50

Table 4: In Vivo hGH (zinc level in all cases was 15 mM)

Formulation	Polymer		Solvent		Drug Particle		Trizma Buffer (mM)
	Level	PLGA	Level	Type	Level	Process	
F	45%	502	45%	BB	10%	L	50
N	45%	502	45%	80%BB/20%TA	10%	L	5
P	45%	502H	45%	TA	10%	L	5
Q	45%	502H	45%	BB	10%	L	5
R	45%	502	45%	EB	10%	L	5
S	45%	502	45%	TC	10%	L	5
T	40%	502	40%	BB	20%	L	5
W	45%	502-2	45%	BB	10%	L	5
X	45%	502	45%	TA	10%	L	5

Example 3 - Lysozyme In Vitro Studies

Lysozyme from chicken egg white (Sigma Chemical Co., St Louis, MO) in vitro release studies were used to test different vehicle formulations with the highly water soluble solvent NMP and the less soluble solvents triacetin and benzyl benzoate useful in the present invention. A depot gel formulation was dispensed from a 3 cc disposable syringe and weighed onto a Delrin™ cup platform or a 250 μ mesh 1 square inch polypropylene screen. Then, the cup or screen containing a depot gel formulation was immersed into a plastic

1 cup or screen containing a depot gel formulation was immersed into a plastic
2 vial containing 10 mL of receptor buffer. A snap-on lid was placed onto the
3 plastic vial to prevent evaporation. The vial containing the depot gel
4 formulation was immersed into a Haake shaking water bath equilibrated to
5 37°C. At each time point, forceps were used to transfer Delrin™ cup
6 platforms or polypropylene screen platforms containing depot gel formulations
7 to new plastic vials containing 10 mL of receptor buffer. Disposable transfer
8 pipettes were used to transfer receptor samples to HPLC vials. The receptor
9 buffer was phosphate buffered saline, PBS, adjusted to pH 7 containing
10 sodium azide (0.2%). Receptor buffers contained tween-80 (0.1%) for most
11 cases. Collection intervals were typically 2, 4, 8 hours, 1, 2, 3, 4, 7, 10 days,
12 and 2, 3, 4, 5, 6, 7, 8 weeks. All receptor samples were analyzed for
13 lysozyme concentration using a gradient elution Reverse-Phase High
14 Performance Liquid Chromatography (RP-HPLC) assay with a refrigerated
15 autosampler (4°C). Results indicated that the compositions of the present
16 invention using benzyl benzoate and benzyl benzoate solvent mixtures
17 exhibited substantially less burst of lysozyme than that exhibited by the gel
18 compositions formed with NMP.

19 Example 4 - In Vitro Water Content Studies

20 The same procedure was used as described in Example 3 for in vitro drug
21 release using the Delrin™ cup platform, except the entire cup platform
22 containing the depot gel vehicle was removed, blotted dry, and placed in a
23 dry plastic vial at specified time intervals. The receptor solution was sterile
24 water and replaced at each time interval for the remaining samples. Initial

1 and final depot gel vehicle weights were recorded to observe weight change.
2 Water content was obtained from depot gel vehicles using a Karl Fischer
3 Apparatus, Mitsubishi Moisture Meter CA-06 equipped with Vaporizer VA-06.
4 Results are illustrated in Figures 4A-4B for selected gels. Those results
5 demonstrate that gel compositions of this invention take up substantially less
6 water than gel compositions formed with NMP alone.

7 Example 5 - hGH In Vivo Studies

8 In vivo studies in rats were performed following an open protocol to determine
9 serum levels of hGH upon systemic administration of hGH via the implant
10 systems of this invention. Depot gel hGH formulations, spray-dried (SD) or
11 lyophilized (L), were loaded into customized 0.5 cc disposable syringes.
12 Disposable 16 gauge needles were attached to the syringes and were heated
13 to 37°C using a circulator bath. Depot gel hGH formulations were injected
14 into rats and blood was drawn at specified time intervals. All serum samples
15 were stored at 4°C prior to analysis. Samples were analyzed for intact hGH
16 content using a radio immuno assay (RIA). Representative results for
17 triacetin and benzyl benzoate are illustrated in Figures 5A and 5B, and
18 demonstrate the superior control of burst by the compositions of the present
19 invention.

20 Example 6

21 Implant systems of this invention are prepared in accordance with
22 Example 2 with equivalent quantities of interferon alpha-2a and -2b,
23 consensus interferon, methionine human growth hormone, des-phenylalanine
24 human growth hormone, carboplatin and insulin-like growth factor. The

1 amount of the viscous gel containing drug administered to rats in accordance
2 with Example 5 is adjusted to take into account the relative biological activity
3 of the separate agents. The implant systems are implanted in rats to provide
4 systemic levels of active agent.

5 Example 7

6 Implant systems containing carboplatin are prepared according to
7 Example 6 and injected directly into solid tumors of tumor bearing rats. The
8 implant systems are suitable for local delivery of carboplatin to tumors.

9 Example 8

10 100 Mg implantable depots containing 0.5, 1.5 and 3 mg of interferon
11 alpha-2b, stabilized with 0.5, 1 and 2 mg of sucrose, respectively, and the
12 remainder being 50 mg benzyl benzoate and 45-49 mg of PLGA 502 as
13 applicable (number average molecular weight of about 10,000) are prepared
14 in accordance with Example 2 (without the addition of zinc). The implants
15 exhibit limited burst and are suitable for implantation. The implant systems
16 are implanted in rats to provide systemic levels of interferon alpha-2b.

17 In accordance with various aspects of the present invention, one or
18 more significant advantages can be obtained. More specifically, implantable
19 or injectable viscous gels containing beneficial agent for systemic and local
20 administration are obtained that exhibit low or minimal burst effect when
21 implanted. Furthermore, using simple processing steps, one can obtain a gel
22 composition that can be surgically implanted in an animal or injected into
23 place in an animal without surgery using a low dispensing force through
24 standard needles. Once in place, the composition will substantially avoid a

1 burst effect and provide the desired beneficial agent release profile.
2 Furthermore, once the beneficial agent has been fully administered, there is
3 no need to remove the composition since it is fully biodegradable. As a still
4 further advantage, the present invention avoids the use of microparticle or
5 microencapsulation techniques which can degrade certain beneficial agents,
6 like peptide and nucleic acid-based drugs and which microparticles and
7 microcapsules may be difficult to remove from the environment of use. Since
8 the viscous gel is formed without the need for water, temperature extremes,
9 or other solvents, suspended particles of beneficial agent remain dry and in
10 their original configuration, which contributes to the stability of thereof.
11 Further, since a mass is formed, the injectable depot gel composition may be
12 retrieved from the environment of use if desired.

13 The above-described exemplary embodiments are intended to be
14 illustrative in all respects, rather than restrictive, of the present invention.
15 Thus the present invention is capable of many variations in detailed
16 implementation that can be derived from the description contained herein by
17 a person skilled in the art. All such variations and modifications are
18 considered to be within the scope and spirit of the present invention as
19 defined by the following claims.

1 WE CLAIM:

2 1. A method of systemically administering a beneficial agent to a
3 subject which comprises implanting a system comprising a beneficial agent
4 dissolved or dispersed substantially throughout a viscous gel, the system
5 having a burst index of 8 or less.

6 2. The method of Claim 1 wherein the viscous gel comprises a
7 biocompatible polymer and a solvent.

8 3. The method of Claim 2 in which the viscous gel optionally includes
9 one or more of the following: an emulsifying agent, a pore former, a solubility
10 modulator for the beneficial agent and an osmotic agent.

11 4. The method of Claim 2 wherein the solvent comprises a solvent
12 having a miscibility in water of less than 7% by weight.

13 5. The method of Claim 4 wherein the solvent is selected from lower
14 alkyl and aralkyl esters of aryl acids; aryl, aralkyl and lower alkyl ketones; and
15 lower alkyl esters of citric acid.

16 6. The method of Claim 2 wherein the polymer is selected from the
17 group consisting of polylactides, polyglycolides, polycaprolactones,
18 polyanhydrides, polyamines, polyurethanes, polyesteramides,
19 polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates,
20 polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid),
21 poly(amino acids), polyvinylpyrrolidone, polyethylene glycol,
22 polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and
23 mixtures thereof.

1 7. The method of Claim 5 wherein the polymer is a lactic acid-based
2 polymer and the solvent is selected from lower alkyl and aralkyl esters of
3 benzoic acid.

4 8. A method of locally administering a beneficial agent to a subject
5 which comprises implanting a system comprising a beneficial agent dissolved
6 or dispersed substantially throughout a viscous gel, the system releasing
7 within 24 hours after implantation not greater than 20% by weight of the
8 amount of beneficial agent to be delivered over the duration of the delivery
9 period.

10 9. The method of Claim 8 wherein the viscous gel comprises a
11 biocompatible polymer and a solvent.

12 10. The method of Claim 9 in which the viscous gel optionally includes
13 one or more of the following: an emulsifying agent, a pore former, a solubility
14 modulator for the beneficial agent, and an osmotic agent.

15 11. The method of Claim 10 wherein the solvent comprises a solvent
16 having a miscibility in water of less than 7% by weight.

17 12. The method of Claim 11 wherein the solvent is selected from
18 lower alkyl and aralkyl esters of aryl acids; aryl, aralkyl and lower alkyl
19 ketones; and lower alkyl esters of citric acid.

20 13. The method of Claim 9 wherein the polymer is selected from the
21 group consisting of polylactides, polyglycolides, polycaprolactones,
22 polyanhydrides, polyamines, polyurethanes, polyesteramides,
23 polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates,
24 polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid),

1 poly(amino acids), polyvinylpyrrolidone, polyethylene glycol,
2 polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and
3 mixtures thereof.

4 14. The method of Claim 12 wherein the polymer is a lactic acid-
5 based polymer and the solvent is selected from lower alkyl and aralkyl esters
6 of benzoic acid.

7 15. A method of administering a beneficial agent to a subject in a
8 controlled manner approximating zero order release by implanting a gel
9 composition comprising a biocompatible polymer, a biocompatible solvent
10 having a solubility in water of less than 7%, and a beneficial agent, wherein
11 the loading of the beneficial agent in the interior of the polymer is above that
12 required to saturate the beneficial agent in water.

13 16. A method of administering a beneficial agent to a subject which
14 comprises implanting a system comprising a beneficial agent dissolved or
15 dispersed substantially throughout a viscous gel formed of a biocompatible
16 polymer and a solvent having a solubility in water of 7% or less, and a
17 solubility modulator of the beneficial agent, the system having a burst index of
18 8 or less.

19 17. The method of Claim 16 wherein the polymer is a lactic acid-
20 based polymer.

21 18. An implantable composition for the systemic delivery of a
22 beneficial agent to a subject wherein the composition comprises a polymer;
23 an amount of a solvent to form a viscous gel with the polymer, and a
24 beneficial agent dissolved or dispersed in the gel, wherein the solvent

1 comprises a single solvent or a mixture of solvents with at least one solvent
2 having a miscibility in water of less than 7% by weight and the total amount of
3 solvent constituting 40% or more by weight of the gel vehicle, said
4 composition having a burst index of 8 or less.

5 19. An implantable, biodegradable composition for the sustained
6 delivery of a beneficial agent to a subject wherein the composition comprises
7 a polymer; an effective plasticizing amount of a solvent to form a viscous gel
8 with the polymer; and a beneficial agent dissolved or dispersed in the gel,
9 wherein the solvent comprises a mixture of solvents with at least one solvent
10 in the mixture having a miscibility in water of less than 7% by weight.

11 20. The composition of Claim 19 wherein the miscibility in water of the
12 solvent mixture is 10% or less by weight.

13 21. An implantable, biodegradable composition for delivery of a
14 beneficial agent to a subject wherein the composition comprises a polymer;
15 an effective plasticizing amount of a solvent to form a viscous gel with the
16 polymer; and a beneficial agent dissolved or dispersed in the gel, wherein the
17 solvent comprises a single solvent or a mixture of solvents with at least one
18 solvent having a miscibility in water of less than 7% by weight selected from
19 lower alkyl and aralkyl esters of benzoic acid.

20 22. An implantable gel composition for delivery of a beneficial agent to
21 a subject comprising:

22 A) a biocompatible polymer;

1 D) an emulsifying agent;

2 E) a pore former;

3 F) a solubility modulator for the beneficial agent; and

4 G) an osmotic agent.

5 24. The composition of Claim 23 wherein R_1 is phenyl.

6 25. The composition of Claim 24 wherein R_2 is benzyl.

7 26. A method of preparing an injectable depot gel composition comprising:

8 A) mixing a biocompatible polymer and a solvent having a miscibility in water of
9 7% or less selected from lower alkyl and aralkyl esters of benzoic acid to form a
10 viscous gel;

11 B) dispersing or dissolving a beneficial agent, optionally associated with a
12 solubility modulator, in an emulsifying agent to form a beneficial agent containing
13 emulsifying agent; and

14 C) mixing the beneficial agent containing emulsifying agent with the viscous
15 gel, said beneficial agent containing emulsifying agent forming a dispersed droplet
16 phase in the viscous gel, and optionally,

17 D) mixing one or more of a pore former and an osmotic agent with said
18 viscous gel, to provide an injectable gel composition.

19 27. A gel composition for systemic administration comprising:

20 A) a biocompatible polymer;

21 B) a biocompatible solvent having a miscibility in water of less than 7%;

1 C) a beneficial agent selected from the group consisting of cDNA, DNA,
2 peptides, proteins and fragments and derivatives thereof, and optionally, one or more
3 of the following:

4 D) an emulsifying agent;

5 E) a pore former;

6 F) a solubility modulator for the beneficial agent; and

7 G) an osmotic agent.

8 wherein the composition has a burst index of less than 8.

9 28. A kit for administration of a beneficial agent to a subject comprising:

10 A) a biocompatible polymer;

11 B) a solvent having a miscibility in water of 7% or less by weight that is suitable
12 for dissolving the polymer and forming a viscous gel;

13 C) a beneficial agent; and optionally, one or more of the following:

14 D) an emulsifying agent;

15 E) a pore former;

16 F) a solubility modulator for the beneficial agent, optionally associated with the
17 beneficial agent; and

18 G) an osmotic agent;

19 wherein at least the beneficial agent, optionally associated with the solubility
20 modulator, is maintained separated from the solvent until the time of administration of
21 the beneficial agent to a subject.

22 29. An implantable composition for the systemic delivery of a beneficial agent
23 comprising a poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a

1 solvent to form a viscous gel with the polymer; and a beneficial agent selected from the
2 group consisting of cDNA, DNA, peptides, proteins and fragments and derivatives
3 thereof, said composition having a burst index of equal to or less than 8.

4 30. An implantable composition for the sustained delivery of a beneficial agent
5 comprising a poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a
6 solvent comprising a lower alkyl or aralkyl ester of benzoic acid to form a viscous gel
7 with the polymer; and a beneficial agent.

8 31. The composition of Claim 30 wherein the solvent has a miscibility in water
9 by weight of less than 7%.

10 32. The composition of Claim 30 wherein the solvent is benzyl benzoate.

11 33. The composition of Claim 30 comprising a solubility modulator of the
12 beneficial agent.

13 34. The composition of Claim 30 comprising a pore former.

14 35. The composition of Claim 30 comprising an emulsifying agent.

15 36. The composition of Claim 30 comprising an osmotic agent.

16 37. The composition of Claim 33 wherein the solubility modulator is selected
17 from salts of divalent metals.

18 38. The composition of Claim 34 in which the pore former is water soluble.

19 39. The composition of Claim 34 wherein the pore former is selected from group
20 consisting of water soluble sugars, salts, solvents and polymers.

21 40. The composition of Claim 35 in which the emulsifying agent is capable of
22 forming a dispersed droplet phase in said viscous gel.

41. The composition of Claim 35 in which the emulsifying agent is selected from the group consisting of alcohols, propylene glycol, ethylene glycol, glycerol, water and solutions and mixtures thereof.

42. The composition of Claim 35 wherein the emulsifying agent is selected from the group consisting of ethanol, isopropyl alcohol, water, solutions thereof, and mixtures thereof.

43. The composition of Claim 30 wherein the copolymer has a monomer ratio of lactic acid to glycolic acid in the range of 100:0 to about 15:85.

44. The composition of Claim 30 wherein the copolymer has a number average molecular weight of from 1,000 to 120,000.

45. The composition of Claim 30 wherein the solvent comprises a component solvent miscible with the solvent.

46. The composition of Claim 45 wherein the component solvent is selected from the group consisting of triacetin, diacetin, tributyrin, triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides, triethyl phosphate, diethyl phthalate, diethyl tartrate, mineral oil, polybutene, silicone fluid, glylcerin, ethylene glycol, polyethylene glycol, octanol, ethyl lactate, propylene glycol, propylene carbonate, ethylene carbonate, butyrolactone, ethylene oxide, propylene oxide, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one, and mixtures thereof.

1 47. The composition of Claim 45 wherein the component solvent is selected
2 from the group consisting of triacetin and N-methyl-2-pyrrolidone, and mixtures thereof.

3 48. The composition of Claim 45 wherein the component solvent is triacetin.

4 49. The method of Claim 2 wherein the beneficial agent is present in an amount
5 of from 1 to 50% by weight of the combined amounts of the polymer, the solvent and
6 the beneficial agent.

7 50. The method of Claim 1 wherein the beneficial agent is cDNA, DNA, a
8 protein, a peptide, and derivatives or fragments thereof, or a chemotherapeutic agent.

9 51. The method of Claim 50 wherein the beneficial agent is human growth
10 hormone, methionine-human growth hormone, des-phenylalanine human growth
11 hormone, interferon alpha-2a, interferon alpha-2b, or consensus interferon.

12 52. The method of Claim 8 wherein the beneficial agent is cDNA, DNA, a
13 protein, a peptide, and derivatives or fragments thereof, or a chemotherapeutic agent.

14 53. The method of Claim 1 wherein the beneficial agent is released from the
15 system over a prolonged period.

16 54. The method of Claim 8 wherein the beneficial agent is released from the
17 system over a prolonged period.

18 55. The method of Claim 1 wherein the system is non-rigid after implantation.

19 56. The method of Claim 55 wherein the system maintains a glass transition
20 temperature below 37°C for at least 24 hours after implantation.

21 57. The method of Claim 9 wherein the system is non-rigid after implantation.

22 58. The method of Claim 57 wherein the system maintains a glass transition
23 temperature below 37°C for at least 24 hours after implantation.

1 59. The composition of Claim 18 wherein the gel remains non-rigid after
2 implantation.

3 60. The composition of Claim 59 wherein the gel maintains a glass transition
4 temperature below 37°C for at least 24 hours after implantation.

5 61. An implantable gel composition comprising a biocompatible polymer, a
6 biocompatible solvent forming a viscous gel with the polymer, and a beneficial agent,
7 the composition imbibing 40% or less of its bulk weight in water within the first 21 days
8 after implantation.

9 62. The composition of Claim 61 wherein the composition imbibes less than
10 30% of its bulk weight in water within the first 14 days after implantation.

11 63. The composition of Claim 62 wherein the composition imbibes less than
12 25% of its bulk weight in water within the first 7 days after implantation.

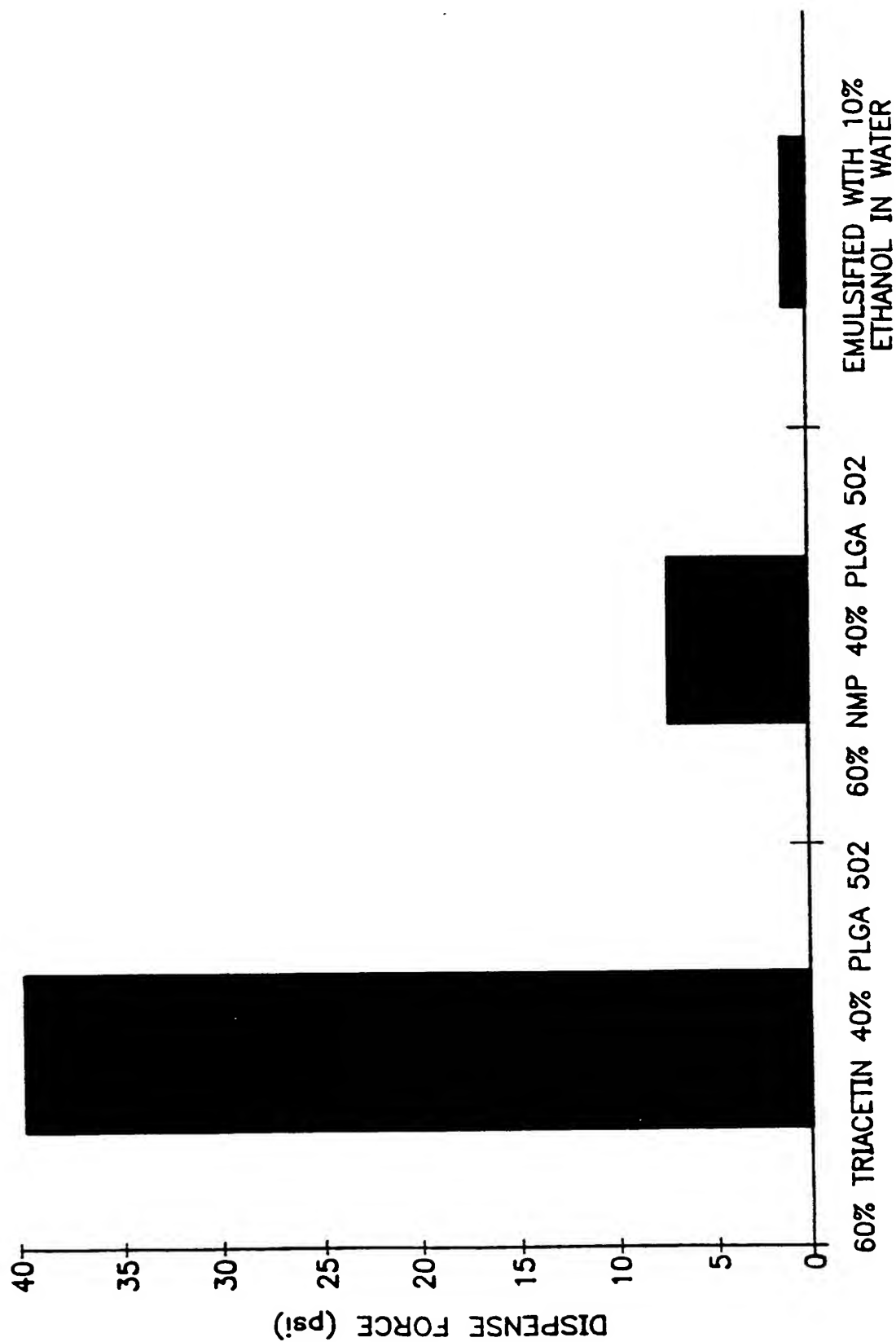


FIG. 1

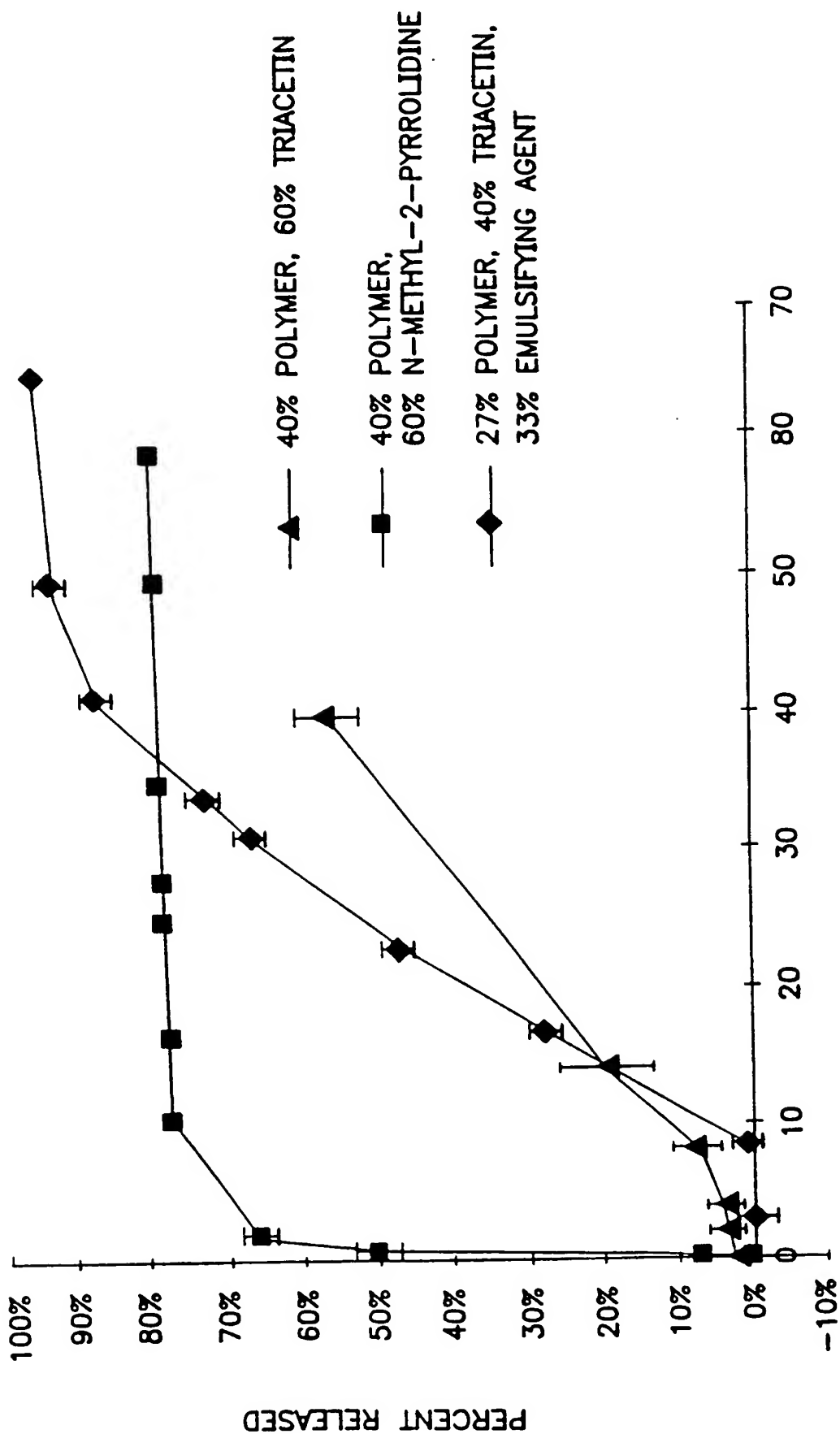


FIG. 2

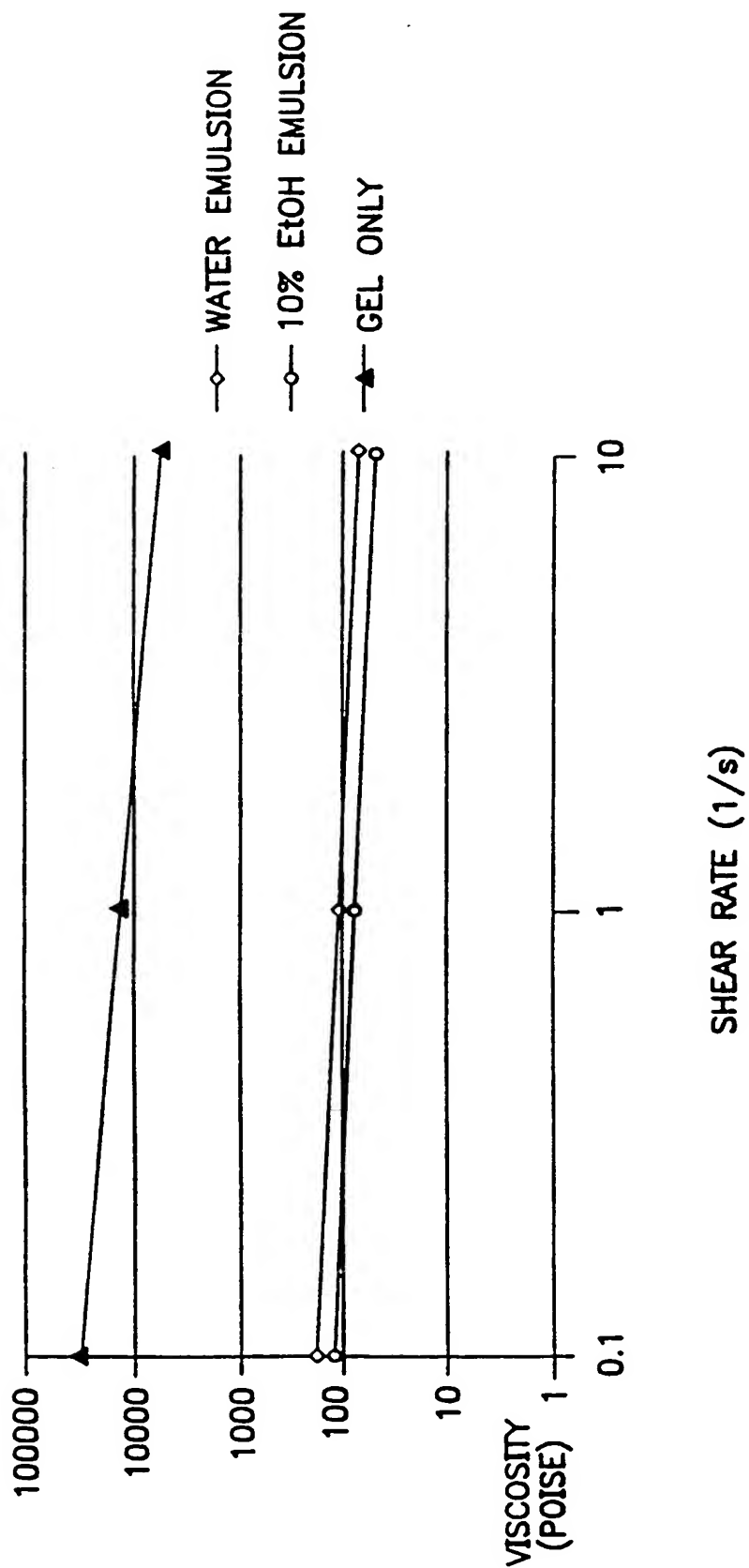


FIG. 3

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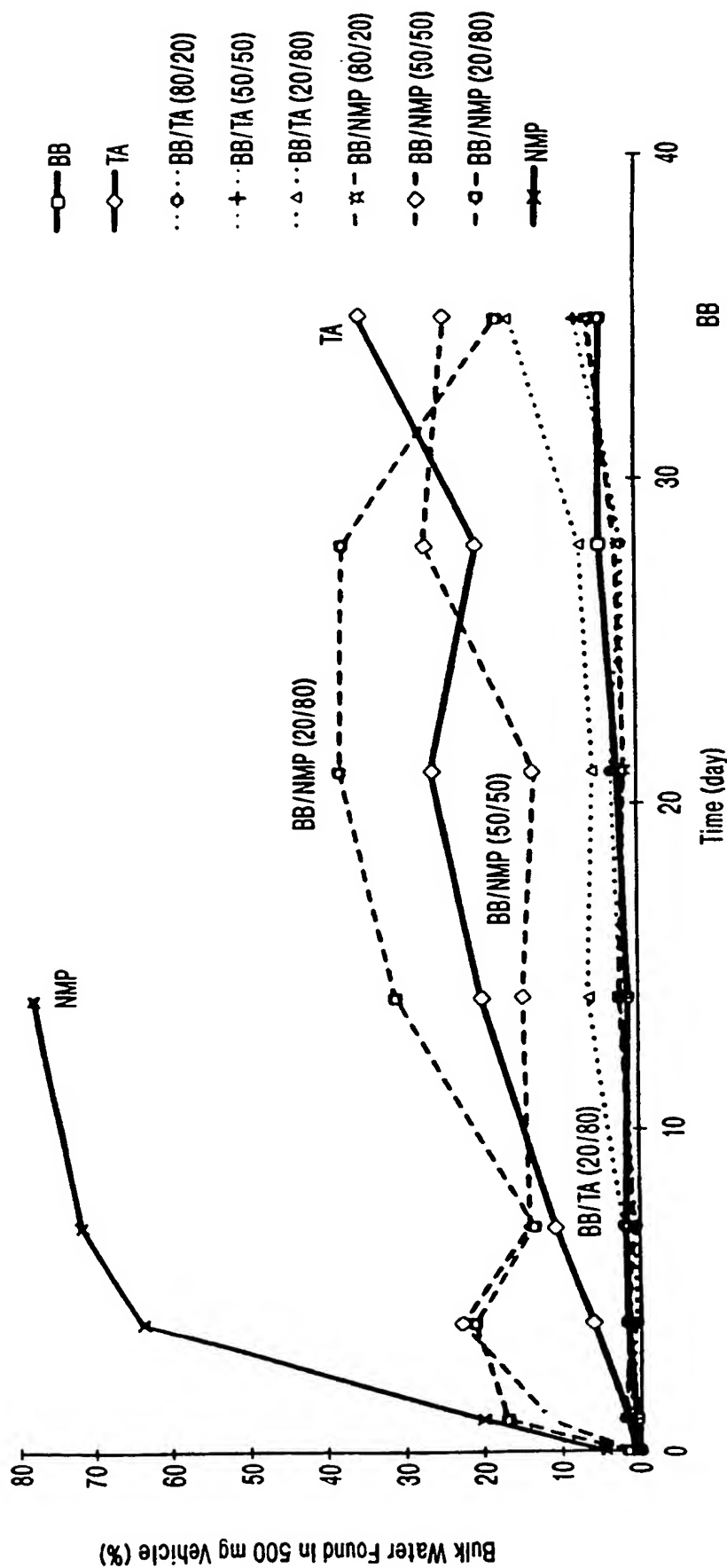


FIG. 4A

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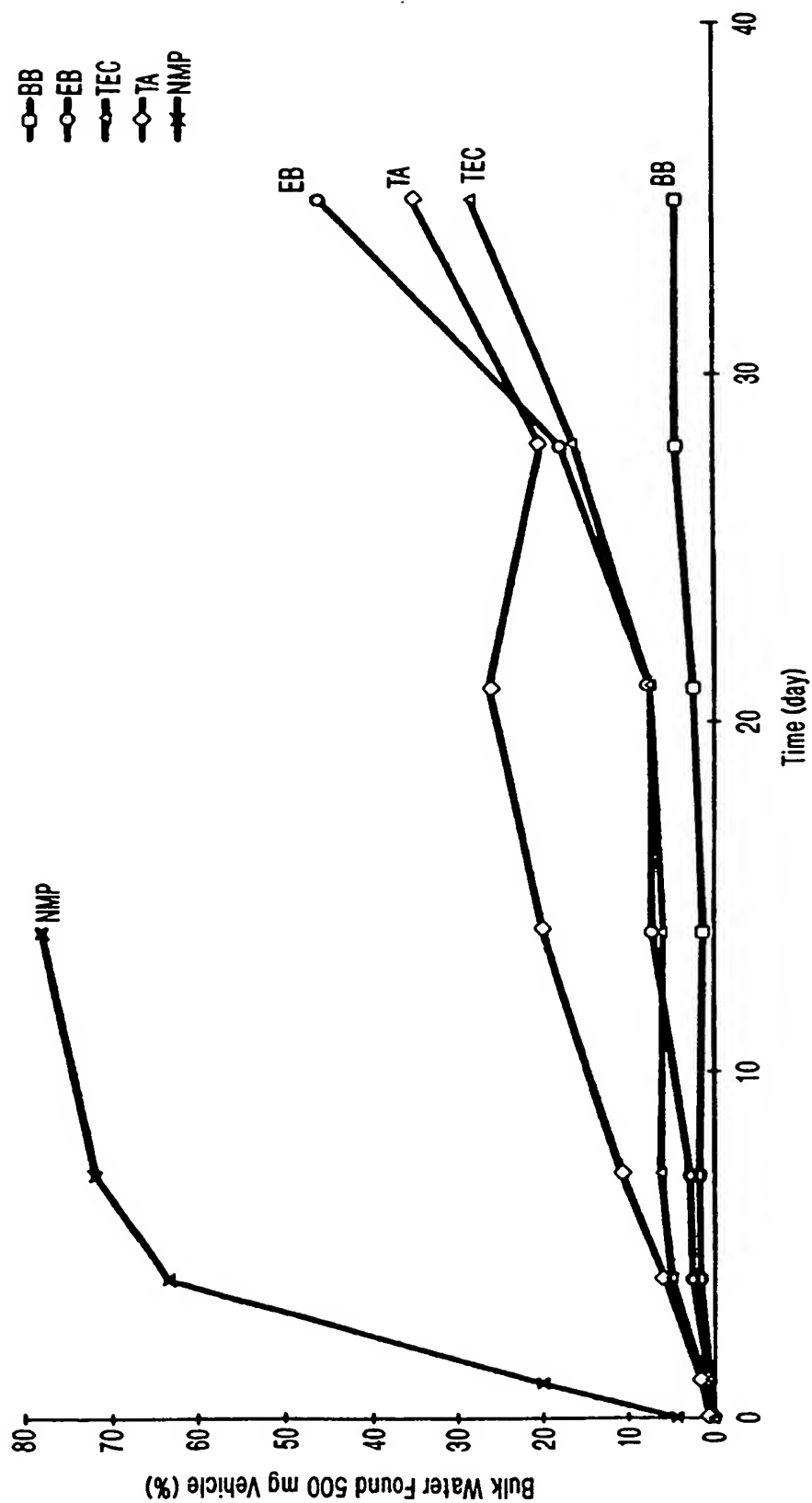


FIG. 4B

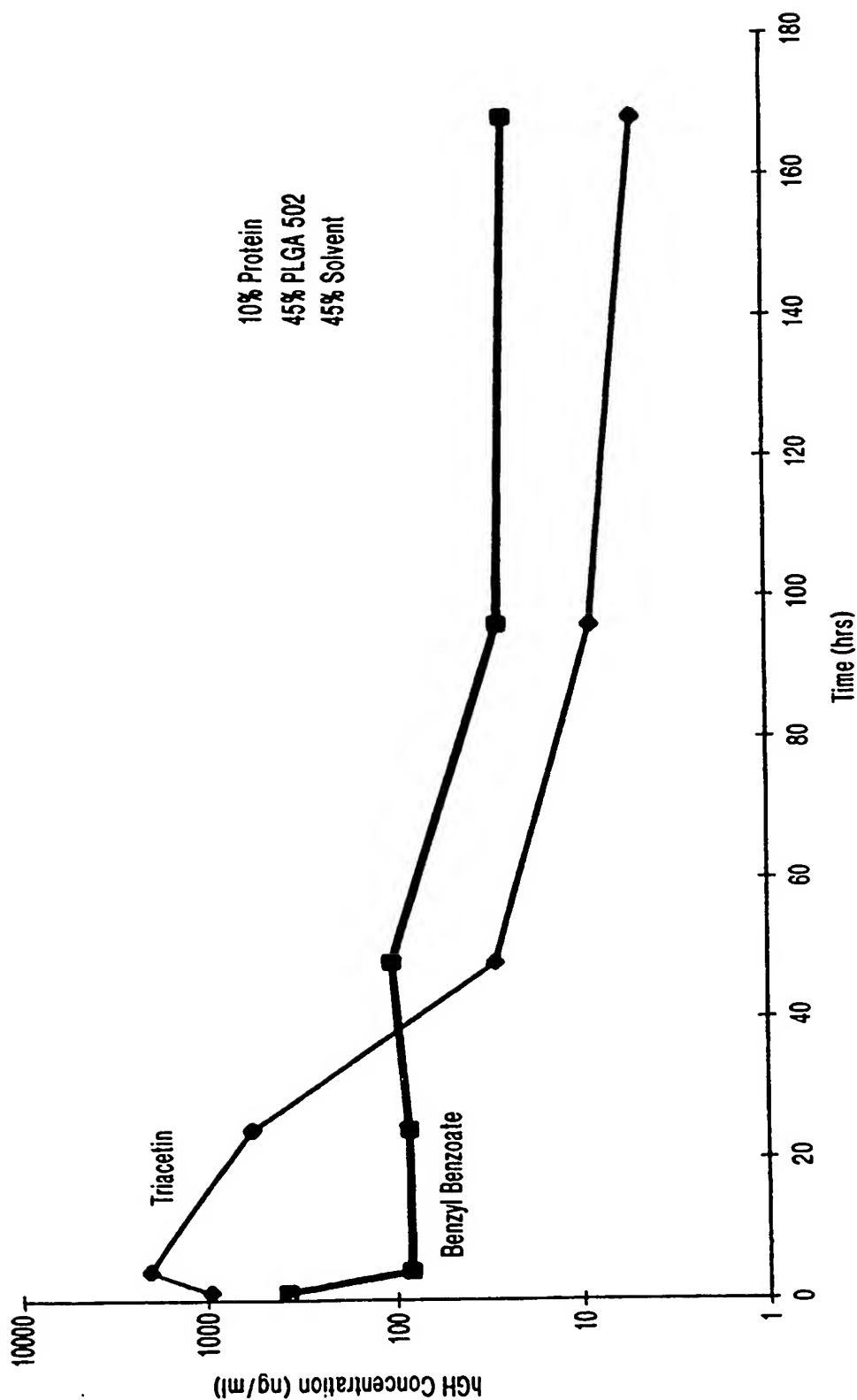


FIG. 5A

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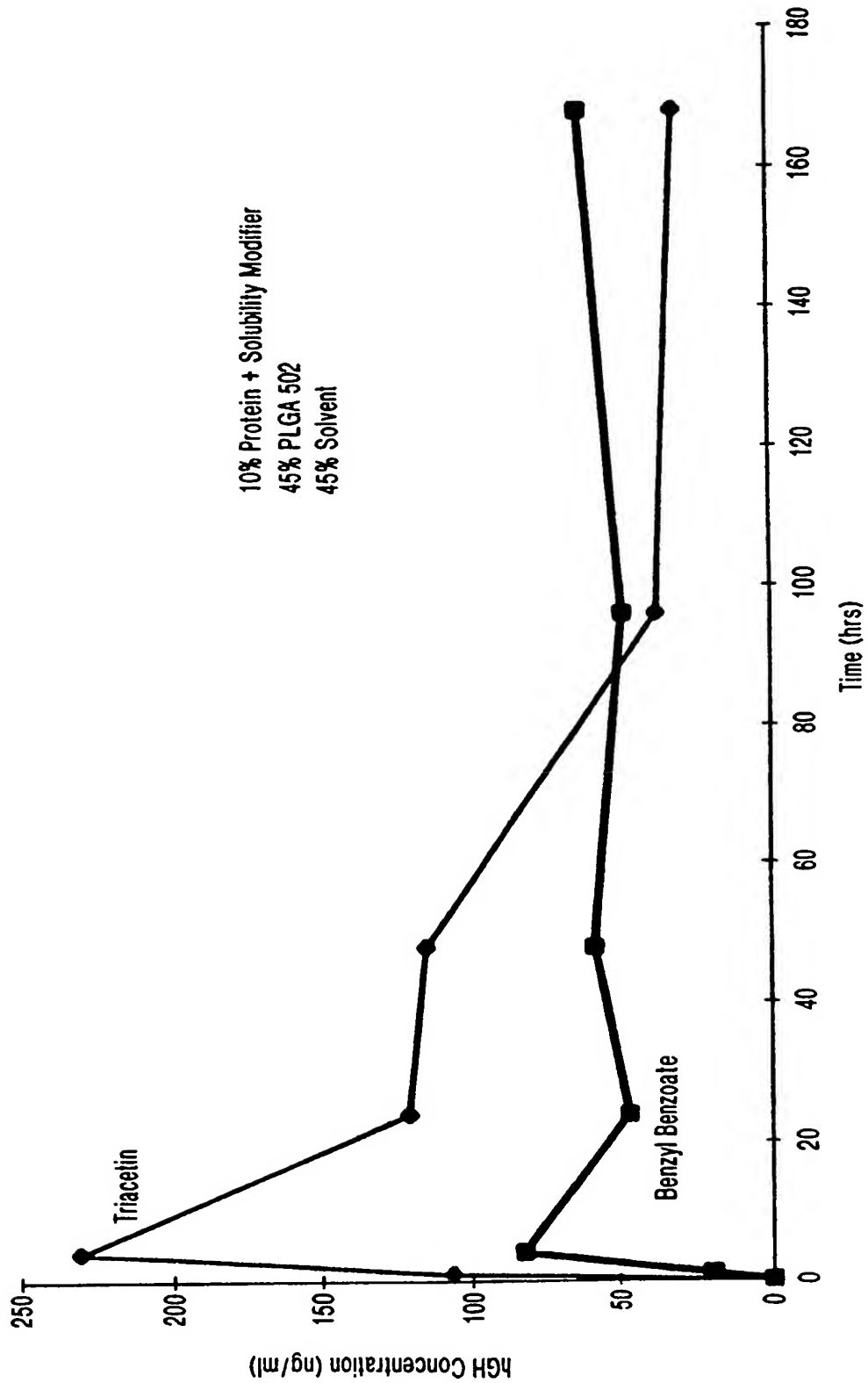


FIG. 5B

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 47/34	A3	(11) International Publication Number: WO 98/27963 (43) International Publication Date: 2 July 1998 (02.07.98)
(21) International Application Number: PCT/US97/23659 (22) International Filing Date: 18 December 1997 (18.12.97) (30) Priority Data: 60/033,439 20 December 1996 (20.12.96) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRODBECK, Kevin, J. [US/US]; 2383 South Court Street, Palo Alto, CA 94301 (US). GAYNOR-DUARTE, Ann, T. [US/US]; 13063 Broadway Terrace, Oakland, CA 94611 (US). SHEN, Theodore, T. [US/US]; 18 Dockside Circle, Redwood City, CA 94065 (US). (74) Agents: DHUEY, John, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 15 October 1998 (15.10.98)
(54) Title: GEL COMPOSITION AND METHODS		
(57) Abstract Methods and compositions for systemically or locally administering by implantation a beneficial agent to a subject are described, and include, for example, compositions having burst indices of 8 or less for systemic applications and systems releasing 10 % or less of the total dose of beneficial agent in the first 24 hours after implantation for local applications. The compositions include a biocompatible polymer, a biocompatible solvent having low water miscibility that forms a viscous gel with the polymer and limits water uptake by the implant, and a beneficial agent.		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23659

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 95 27481 A (ATRIX LABORATORIES INC., U.S.A.) 19 October 1995</p> <p>see claims 1-3, 7, 10-15, 19-27, 30 see page 4, line 26 - line 30 see page 14, line 3 - line 5 see page 14, line 22 - page 15, line 1 see page 18, line 33 - page 19, line 10 see page 26, line 21 - line 25 see page 30, line 12 - line 16</p> <p>--- -/--</p>	<p>1-3, 5, 6, 8-10, 12, 13, 18-20, 27, 29, 49-55, 59</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/23659

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 03768 A (SOUTHERN RESEARCH INSTITUTE, U.S.A.) 19 April 1990 cited in the application see claims 1-10, 27-37, 45 ---	1-6, 16-20, 27, 29, 49, 50, 53, 55
X	US 5 242 910 A (N.C.DAMANJ) 7 September 1993 cited in the application see claims see column 5, line 20 - column 27 see column 5, line 64 - line 67 see examples IV, V, VI ---	1-6, 15-20, 49, 50, 53, 55
X	EP 0 539 751 A (ATRIX LABORATORIES INC., U.S.A.) 5 May 1993 cited in the application see claims ---	1-6, 16-20, 27, 29, 49, 50, 53, 55
X, P	WO 97 15287 A (MACROMED INC., U.S.A.) 1 May 1997 see claims 1, 5, 8, 13-18, 34 see page 21, line 15 - line 18 see page 11, line 5 - line 21 see page 15, line 29 - page 16, line 9 see page 17, line 35 - line 37 see page 22, line 18 - line 24 see page 23, line 1 - line 12 ---	1-3, 6, 29, 49-51, 53, 55, 56
A	WO 91 05544 A (MEDINVENT, SE) 2 May 1991 see claims 1, 2, 10, 12-14, 18 see page 7, line 1 - line 3 see page 4, line 19 - line 31 ---	1-3, 6, 8, 15, 26, 28, 49, 53-55, 61
A	US 5 318 780 A (T.X.VIEGAS ET AL.) 7 June 1994 see claims ----- -/--	1-3, 6, 8, 15, 26, 28, 49, 53-55, 61

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23659

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP 0 640 647 A (COLLAGEN CORPORATION, U.S.A.) 1 March 1995</p> <p>see claims 1,3,5,44,47 see page 3, line 39 - line 41 see page 3, line 50 - line 52 see page 24, line 2 - line 5 see page 24, line 30 - line 34 -----</p>	<p>1-3,6,8, 15,26, 28,49, 53-55,61</p>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 23659

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-17, 49-58
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-17, 49-58
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/23659

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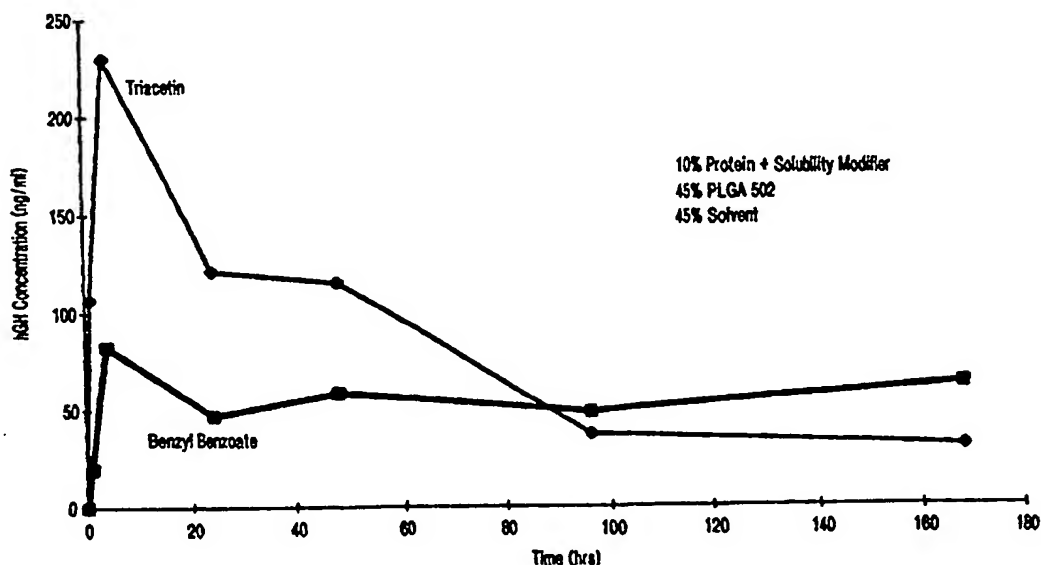
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 47/34	A2	(11) International Publication Number: WO 98/27963 (43) International Publication Date: 2 July 1998 (02.07.98)
(21) International Application Number: PCT/US97/23659 (22) International Filing Date: 18 December 1997 (18.12.97) (30) Priority Data: 60/033,439 20 December 1996 (20.12.96) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRODBECK, Kevin, J. [US/US]; 2383 South Court Street, Palo Alto, CA 94301 (US). GAYNOR-DUARTE, Ann, T. [US/US]; 13063 Broadway Terrace, Oakland, CA 94611 (US). SHEN, Theodore, T. [US/US]; 18 Dockside Circle, Redwood City, CA 94065 (US). (74) Agents: DHUEY, John, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>

(54) Title: GEL COMPOSITION AND METHODS



(57) Abstract

Methods and compositions for systemically or locally administering by implantation a beneficial agent to a subject are described, and include, for example, compositions having burst indices of 8 or less for systemic applications and systems releasing 10 % or less of the total dose of beneficial agent in the first 24 hours after implantation for local applications. The compositions include a biocompatible polymer, a biocompatible solvent having low water miscibility that forms a viscous gel with the polymer and limits water uptake by the implant, and a beneficial agent.

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GEL COMPOSITION AND METHODS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a gel composition that can be implanted into a desired location and which can provide controlled release of a beneficial agent. The present invention also relates to methods of controlling release of a beneficial agent from a composition.

Description of the Related Art

Biodegradable polymers have been used for many years in medical applications. Illustrative devices composed of the biodegradable polymers include sutures, surgical clips, staples, implants, and sustained release drug delivery systems. The majority of these biodegradable polymers have been based upon glycolide, lactide, caprolactone, and copolymers thereof.

The biodegradable polymers can be thermoplastic materials which means that they can be heated and formed into various shapes such as fibers, clips, staples, pins, films, etc. Alternatively, they can be thermosetting materials formed by crosslinking reactions which lead to high-molecular-weight materials that do not melt or form flowable liquids at high temperatures.

Although thermoplastic and thermosetting biodegradable polymers have many useful biomedical applications, there are several important limitations to their use in the bodies of various animals including humans, animals, birds, fish, and reptiles. Because these polymers generally are

1 solids, all instances involving their use have required initially forming the
2 polymeric structures outside the body, followed by insertion of the solid
3 structure into the body. For example, sutures, clips, and staples are all
4 formed from thermoplastic biodegradable polymers prior to use. When
5 inserted into the body, they retain their original shape. While this
6 characteristic is essential for some uses, it is not preferred where it is desired
7 that the material be molded or flow to fill voids or cavities where it may be
8 most needed.

9 Drug delivery systems using thermoplastic or thermosetting
10 biodegradable polymers also often are or have to be formed outside the
11 body. In such instances, the drug is incorporated into the polymer and the
12 mixture is shaped into a certain form such as cylinder, disc, or fiber for
13 implantation. With such solid implants, the drug delivery system has to be
14 inserted into the body through an incision. These incisions are sometimes
15 larger than desired by the medical profession and occasionally lead to a
16 reluctance of the patient to accept such an implant or drug delivery system.
17 Nonetheless, both biodegradable and non-biodegradable implantable drug
18 delivery systems have been widely used successfully.

19 One reservoir device having a rate-controlling membrane and zero-
20 order release of an agent that is particularly designed for intraoral
21 implantation is described in U.S. Patent No. 5,085,866. The device is
22 prepared from a core that is sprayed with a solution having a polymer and a
23 solvent that is composed of a rapidly evaporating, low boiling point first
24 solvent and a slowly evaporating, high boiling point second solvent.

1 Other illustrative osmotic delivery systems include those disclosed in
2 U.S. Patent Nos. 3,797,492, 3,987,790, 4,008,719, 4,865,845, 5,057,318,
3 5,059,423, 5,112,614, 5,137,727, 5,151,093, 5,234,692, 5,234,693,
4 5,279,608, and 5,336,057. Pulsatile delivery devices are also known which
5 deliver a beneficial agent in a pulsatile manner as disclosed in U.S. Patent
6 Nos. 5,209,746, 5,308,348, and 5,456,679.

7 One way to avoid the incision needed to implant drug delivery systems
8 is to inject them as small particles, microspheres, or microcapsules. For
9 example, U.S. Patent No. 5,019,400 describes the preparation of controlled
10 release microspheres via a very low temperature casting process. These
11 materials may or may not contain a drug which can be released into the body.
12 Although these materials can be injected into the body with a syringe, they do
13 not always satisfy the demand for a biodegradable implant. Because they are
14 particulate in nature, they do not form a continuous film or solid implant with
15 the structural integrity needed for certain prostheses. When inserted into
16 certain body cavities such as a mouth, a periodontal pocket, the eye, or the
17 vagina where there is considerable fluid flow, these small particles,
18 microspheres, or microcapsules are poorly retained because of their small
19 size and discontinuous nature. Further, the particles tend to aggregate and
20 thus their behavior is hard to predict. In addition, microspheres or
21 microcapsules prepared from these polymers and containing drugs for
22 release into the body are sometimes difficult to produce on a large scale, and
23 their storage and injection characteristics present problems. Furthermore,
24 one other major limitation of the microcapsule or small-particle system is their

1 lack of reversibility without extensive surgical intervention. That is, if there
2 are complications after they have been injected, it is considerably more
3 difficult to remove them from the body than with solid implants. A still further
4 limitation on microparticles or microcapsulation is the difficulty in
5 encapsulating protein and DNA-based drugs without degradation caused by
6 denaturing solvents and temperature extremes used during processing.

7 The art has developed various drug delivery systems in response to
8 the aforementioned challenges. For instance, U.S. Patent No. 4,938,763 and
9 its divisional U.S. Patent No. 5,278,201 relate to a biodegradable polymer for
10 use in providing syringeable, in-situ forming, solid biodegradable implants for
11 animals. In one embodiment, a thermoplastic system is used wherein a non-
12 reactive polymer is dissolved in a water soluble biocompatible solvent to form
13 a liquid which is placed in the animal wherein the solvent dissipates to
14 produce the solid implant. Alternatively, a thermosetting system is used
15 wherein effective amounts of a liquid acrylic ester-terminated, biodegradable
16 prepolymer and a curing agent are formed and the liquid mixture is placed
17 within the animal wherein the prepolymer cures to form the solid implant. It is
18 stated that the systems provide a syringeable, solid biodegradable delivery
19 system by the addition of an effective level of a biologically active agent to the
20 liquid before the injection into the animal.

21 U.S. Patent 5,599,552 describes thermoplastic and thermoset polymer
22 compositions that utilize solvents which are miscible to dispersible in water,
23 such as N-methyl-2-pyrrolidone, resulting in polymer solutions capable of
24 quickly absorbing water from surrounding tissue. The polarity of the solvents

1 is described as being effective to provide about at least 10% solubility in
2 water. The polymer matrix systems are described as forming a porous core
3 surrounded by a porous skin.

4 U.S. Patent No. 5,242,910 describes a sustained release composition
5 containing drugs for treating periodontal disease. The composition comprises
6 copolymers of lactide and glycolide, triacetin (as a solvent/plasticizer) and an
7 agent providing relief of oral cavity diseases. The composition can take the
8 form of a gel and can be inserted into a periodontal cavity via a syringe using
9 either a needle or a catheter. As additional optional components, the
10 composition can contain surfactants, flavoring agents, viscosity controlling
11 agents, complexing agents, antioxidants, other polymers, gums, waxes/oils,
12 and coloring agents. One illustrative viscosity controlling agent set forth in
13 one of the examples is polyethylene glycol 400.

14 U.S. Patent No. 5,620,700 describes a polymer-drug matrix, optionally
15 including plasticizers in an amount up to about 30 wt %, for local application
16 of drug in the peridontal cavity. Among the plasticizers listed are, *inter alia*,
17 triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate,
18 diethyl phthalate, diethyl tartrate, ethyl lactate, triacetin and diacetin. The
19 polymer matrix is non-flowable prior to administration and is heated to
20 become flowable so that it may be dispensed into the peridontal cavity where
21 it solidifies. While the patent discusses possible systemic applications by
22 delivery via the ocular sacs of the eye or intravaginal delivery, it does not
23 address the issue of burst of drug or methods of controlling burst.

1 U.S. Patent No. 3,923,939 describes a method of reducing initial burst
2 of an active agent from a delivery device by removing, prior to implantation,
3 active agent from the exterior surface of the delivery device and through a
4 layer of at least 5% of the overall body thickness extending from the exterior
5 surface of the device.

6 U.S. Patent No. 5,556,905 describes degradable thermoplastic
7 compositions which are modified by plasticizers consisting of various partial
8 esters of citric acid.

9 Prior art polymer compositions for injectable implants have used
10 solvent/plasticizers that are very or relatively soluble in aqueous body fluids to
11 promote rapid solidification of the polymer at the implant site and promote
12 diffusion of drug from the implant. However, it has now been observed that a
13 serious problem associated with prior art polymeric implants utilizing water
14 soluble polymer solvents is the rapid migration of water into the polymer
15 composition when the implant is placed in the body and exposed to aqueous
16 body fluids. That characteristic often results in uncontrolled release of
17 beneficial agent that is manifested by an initial, rapid release of beneficial
18 agent from the polymer composition, corresponding to a "burst" of beneficial
19 agent being released from the implant. The burst often results in a
20 substantial portion of the beneficial agent, if not all, being released in a very
21 short time, e.g., hours or 1-2 days. Such an effect can be unacceptable,
22 particularly in those circumstances where sustained delivery is desired, i.e.,
23 delivery of beneficial agent over a period of a week or a month or more, or
24 where there is a narrow therapeutic window and release of excess beneficial

1 agent can result in adverse consequences to the subject being treated, or
2 where it is necessary to mimic the naturally-occurring daily profile of beneficial
3 agents, such as hormones and the like, in the body of the subject being
4 treated.

5 In an attempt to control burst and modulate and stabilize the delivery of
6 the beneficial agent the prior art has coated particles of beneficial agent to
7 retard release into an aqueous environment and extend release of the
8 beneficial agent over time. Alternatively, various stabilizing or release
9 modulating agents, such as metal salts as described in U.S. Patents
10 5,656,297; 5,654,010; 4,985,404 and 4,853,218 have been used.

11 Notwithstanding some success, those methods have not been entirely
12 satisfactory for the large number of beneficial agents that would be effectively
13 delivered by implants, since in many instances the modulation and
14 stabilization effect is the result of the formation of a complex of the metal ion
15 with the beneficial agent. When such complexes do not form, the
16 stabilization/modulation effect may not be adequate to prevent undesirable
17 "burst" of the beneficial agent upon its introduction into the implant site.

18 Additionally, with conventional low viscosity, solvent-based depot
19 compositions comprised of a polymer dissolved in a solvent, another problem
20 which often exists is that the composition solidifies slowly after injection as
21 solvent diffuses from the depot and water migrates into the depot. Since
22 these compositions are relatively non-viscous in order to be injected, a large
23 percentage of drug may be rapidly released as the system forms by diffusion
24 of the solvent, particularly when the beneficial agent is soluble in the solvent

1 and the solvent rapidly disperses into body fluids. Rapid solvent release
2 contributes to the "burst" effect along with depot hardening due to water
3 uptake. In this respect, it is typical for conventional solvent-based
4 compositions to have a drug burst wherein 30-75% of the drug contained in
5 the composition is released within one day of the initial injection.

6 The rapid water uptake into the polymer implant and solvent dispersion
7 into body fluids exhibited by prior art devices often results in implants having
8 pore structures that are non-homogeneous in size and shape. Typically, the
9 surface pores take on a finger-like pore structure extending for as much as
10 1/3 of a millimeter or more from the implant surface into the implant, and such
11 finger-like pores are open at the surface of the implant to the environment of
12 use. The internal pores tend to be smaller and less accessible to the fluids
13 present in the environment of use. Accordingly, when such devices are
14 implanted, the finger-like pores allow very rapid uptake of aqueous body
15 fluids into the interior of the implant with consequent immediate and rapid
16 dissolution of significant quantities of beneficial agent and unimpeded
17 diffusion of beneficial agent into the environment of use, producing the burst
18 effect discussed above.

19 Furthermore, rapid water uptake can result in premature polymer
20 precipitation such that a hardened implant or one with a hardened skin is
21 produced. The inner pores and much of the interior of the polymer containing
22 beneficial agent are shut off from contact with the body fluids and a significant
23 reduction in the release of beneficial agent can result over a not insignificant
24 period of time ("lag time"). That lag time is undesirable from the standpoint of

1 presenting a controlled, sustained release of beneficial agent to the subject
2 being treated. What one observes, then, is a burst of beneficial agent being
3 released in a short time period immediately after implantation, a lag time in
4 which no or very little beneficial agent is being released, and subsequently
5 continued delivery of beneficial agent (assuming beneficial agent remains
6 after the burst) until the supply of beneficial agent is exhausted.

7 SUMMARY OF THE INVENTION

8 The present invention provides a method and an implantable system
9 for systemic and local delivery of a beneficial agent to a subject. The method
10 and system provide controlled release of beneficial agent to the subject being
11 treated and limit the initial burst of beneficial agent from the implant system.
12 Additionally, the invention provides a method of preparing implant systems
13 having restricted initial burst of beneficial agent.

14 In one aspect, the invention comprises a method of administering,
15 locally or systemically, a beneficial agent to a subject which comprises
16 implanting a system comprising a beneficial agent dispersed or dissolved
17 substantially throughout a viscous gel, the system releasing 20% or less by
18 weight of the beneficial agent present in the viscous gel within the first 24
19 hours after implantation in the subject. Preferably, 10% or less by weight of
20 the beneficial agent will be released within the first 24 hours after
21 implantation.

22 In another aspect, the invention comprises a method of systemically
23 administering a beneficial agent to a subject which comprises implanting a

1 system comprising a beneficial agent dispersed or dissolved substantially
2 throughout a viscous gel, the system having a burst index of 8 or less.

3 In still another aspect, the invention comprises a method of
4 systemically administering a beneficial agent to a subject in a controlled
5 manner approximating zero order release by implanting a gel composition
6 comprising a biocompatible polymer, a biocompatible solvent having a
7 solubility in water of less than 7% and forming a viscous gel with the polymer,
8 and a beneficial agent, wherein the loading of the beneficial agent in the
9 interior of the polymer gel is above that required to saturate the beneficial
10 agent in water.

11 In still another aspect, the invention comprises an implantable,
12 biodegradable composition for the systemic delivery of a beneficial agent to a
13 subject wherein the composition comprises a polymer; an amount of a solvent
14 to form a viscous gel with the polymer, and a beneficial agent dissolved or
15 dispersed in the gel, wherein the solvent comprises a single solvent or a
16 mixture of solvents with at least one solvent having a miscibility in water of
17 less than 7% by weight and the amount of solvent constituting 40% or more
18 by weight of the gel vehicle.

19 In a further aspect, the present invention comprises an implantable,
20 biodegradable composition for the sustained delivery of a beneficial agent to
21 a subject wherein the composition comprises a polymer; an effective
22 plasticizing amount of a solvent to form a viscous gel with the polymer; and a
23 beneficial agent dissolved or dispersed in the gel, wherein the solvent
24 comprises a mixture of solvents with at least one solvent in the mixture

12 In another aspect the present invention provides an implantable gel
13 composition for systemic delivery of a beneficial agent to a subject
14 comprising:

- 20 O

21 $\text{R}_1 - \text{C} - \text{O} - \text{R}_2$

1 and

2

O

3



4 wherein R_1 is lower alkyl, aryl or aralkyl and R_2 is aralkyl or lower alkyl; and R_1
5 and R_2 may be the same or different; with the proviso that when R_1 and R_2 are
6 each lower alkyl, the number of total carbon atoms represented by R_1 and R_2
7 combined is 4 or more;

8 C) a beneficial agent; and, optionally, one or more of the following:

9 D) an emulsifying agent;

10 E) a pore former;

11 F) a solubility modulator of the beneficial agent; and

12 G) an osmotic agent.

13

14 In another aspect the present invention provides an implantable gel
15 composition comprising:

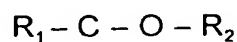
16 A) a biocompatible polymer;

17 B) a biocompatible solvent having miscibility in water of less than
18 7% by weight and capable of dissolving the polymer and forming a viscous
19 gel, said solvent being selected from the group comprising compounds
20 having the following structural formula:

21

O

22



23 wherein R_1 and R_2 are as defined above.

1 In a further aspect, the present invention provides a method of
2 restricting uptake of water by a gel composition which comprises forming the
3 gel composition from a polymer and a solvent that forms a viscous gel with
4 the polymer, the solvent having a miscibility in water of less than 7% by
5 weight. Preferably, the solvent will have a miscibility in water of 6% or less by
6 weight, and more preferably 5% or less by weight.

7 In another aspect, the present invention provides a method of
8 preparing an injectable gel composition comprising:

9 A) mixing a biocompatible polymer and a solvent having a miscibility in
10 water of 7% or less selected from lower alkyl and aralkyl esters of benzoic
11 acid to form a viscous gel;

12 B) dispersing or dissolving a beneficial agent, optionally associated
13 with a solubility modulator of the beneficial agent, in an emulsifying agent to
14 form a beneficial agent containing emulsifying agent; and

15 C) mixing the beneficial agent containing emulsifying agent with the
16 viscous gel, said beneficial agent containing emulsifying agent forming a
17 dispersed droplet phase in the viscous gel, and optionally,

18 D) mixing one or more of a pore former and an osmotic agent with
19 said viscous gel.

20 In another aspect, the present invention provides a method of
21 preparing an implantable gel composition comprising:

22 A) mixing a biocompatible polymer and a solvent having a miscibility in
23 water of 7% or less selected from lower alkyl and aralkyl esters of
24 benzoic acid to form a viscous gel;

1 B) dispersing or dissolving a beneficial agent, optionally associated
2 with a solubility modulator of the beneficial agent, in the viscous
3 gel; and;

4 C) optionally mixing one or more of the following: an emulsifying
5 agent, a pore former, a solubility modulator of the beneficial agent
6 and an osmotic agent, with the beneficial agent containing gel.

7 In yet another aspect, the invention provides a gel composition
8 comprising:

9 A) a biocompatible polymer;

10 B) a biocompatible solvent having a miscibility in water of less than
11 7% by weight;

12 C) a beneficial agent selected from the group consisting of cDNA,
13 DNA, peptides, proteins and fragments and derivatives thereof, and
14 optionally, one or more of the following:

15 D) an emulsifying agent;

16 E) a pore former;

17 F) a solubility modulator of the beneficial agent; and

18 G) an osmotic agent;

19 wherein the composition has a burst index of less than 8.

20 In still another aspect, the invention comprises a kit for administration
21 of a beneficial agent to a subject comprising:

22 A) a biocompatible polymer;

23 B) a solvent having a miscibility in water of 7% or less by weight that is
24 suitable for dissolving the polymer and forming a viscous gel;

- 1 C) a beneficial agent; and optionally, one or more of the following:
- 2 D) an emulsifying agent;
- 3 E) a pore former;
- 4 F) a solubility modulator of the beneficial agent, optionally associated
- 5 with the beneficial agent; and
- 6 G) an osmotic agent;
- 7 wherein at least the beneficial agent, optionally associated with the solubility
- 8 modulator, is maintained separated from the solvent until the time of
- 9 administration of the beneficial agent to a subject.

10 In still another aspect, the invention comprises an implantable

11 composition for the systemic delivery of a beneficial agent comprising a

12 poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a

13 solvent to form a viscous gel with the polymer; and a beneficial agent

14 selected from the group consisting of cDNA, DNA, peptides, proteins and

15 fragments and derivatives thereof, said composition having a burst index of 8

16 or less.

17 In another aspect, the invention comprises an implantable composition

18 for the sustained delivery of a beneficial agent comprising a poly(lactide-co-

19 glycolide) copolymer; an effective plasticizing amount of a solvent selected

20 from lower alkyl and aralkyl esters of benzoic acid to form a viscous gel with

21 the polymer; and a beneficial agent.

22 In a further aspect, the invention comprises an implantable

23 composition comprising a viscous gel and a beneficial agent dispersed or

1 dissolved therein, wherein the viscous gel maintains a glass transition
2 temperature of less than 37°C for at least the first 24 hours after implantation.

3 In yet another aspect, the invention comprises a method of
4 administering a beneficial agent to a subject which comprises implanting a
5 system comprising a beneficial agent dissolved or dispersed substantially
6 throughout a viscous gel formed of a biocompatible polymer and a solvent
7 having a solubility in water of 7% or less, and a solubility modulator of the
8 beneficial agent, the system having a burst index of 8 or less.

9 In a further aspect, the invention comprises an implantable system
10 comprising a beneficial agent dissolved or dispersed substantially throughout
11 a viscous gel formed of a biocompatible polymer and a solvent having a
12 solubility in water of 7% or less, and a solubility modulator of the beneficial
13 agent, the system having a burst index of 8 or less.

14

15 BRIEF DESCRIPTION OF THE DRAWINGS

16 The foregoing and other objects, features and advantages of the
17 present invention will be more readily understood upon reading the following
18 detailed description in conjunction with the drawings in which:

19 Figure 1 is a graph illustrating the dispense force required to dispense
20 emulsified and non-emulsified viscous gel compositions through a 20 gauge
21 needle in psig at 2 cc/min;

22 Figure 2 is a graph illustrating the *in vitro* release profiles of lysozyme
23 from three different compositions in days;

1 Figure 3 is a graph illustrating the viscosity profiles of emulsions at
2 different shear rates of water alone and of an aqueous mixture of ethanol,
3 and of the viscous gel without emulsifying agent;

4 Figures 4A and 4B are graphs illustrating the degree of water uptake
5 for various polymer-solvent mixtures, some of which form a part of this
6 invention, and demonstrating that as the miscibility of the solvent in water
7 decreases, the amount of water taken up into the implant decreases; and

8 Figures 5A and 5B are graphs of *in vivo* release rate profiles of non-
9 stabilized and zinc-stabilized human growth hormone from gels formed from
10 PLGA and the solvents triacetin and benzyl benzoate, respectively.

11 DETAILED DESCRIPTION OF THE INVENTION

12 The present invention is directed to a method of systemically or locally
13 administering a beneficial agent to a subject by implanting in the subject an
14 implantable system, formed as a viscous gel from a biocompatible polymer
15 and a biocompatible solvent, and a beneficial agent is substantially dissolved
16 or dispersed throughout the gel. By appropriate choice of solvent, water
17 migration from the aqueous environment surrounding the implant system is
18 restricted, and beneficial agent is released to the subject over a prolonged
19 period of time, thus providing for delivery of the beneficial agent with a
20 controlled burst of beneficial agent and sustained release thereafter.

21 It has been discovered that when a solvent having a solubility in water
22 of less than 7% by weight in water is present in the system, suitable burst
23 control and sustained delivery of beneficial agent is achieved, whether or not
24 a solubility modulator of the beneficial agent is present in the system.

1 Typically, the implant systems useful in this invention will release, in the first
2 24 hours after implantation, 20% or less of the total amount of beneficial
3 agent to be delivered to the subject from the implant system, preferably 15%
4 or less and more preferably 10% or less. The viscous gel formed preferably
5 is bioerodible so that the implant system does not have to be surgically
6 removed after beneficial agent is depleted from the implant.

7 Water uptake and burst may be controlled by using polymer-solvent
8 compositions wherein the solvent is substantially immiscible in water, i.e., less
9 than 7% by weight soluble in water, so as to control the rate of water
10 migration into the polymer implant and ultimately control the burst of
11 beneficial agent and the sustained delivery of beneficial agent. Generally, the
12 compositions of the invention will be gel-like and will form with a substantially
13 homogeneous pore structure throughout the implant upon implantation and
14 during drug delivery, even as it hardens. Furthermore, while the polymer gel
15 implant will slowly harden when subjected to an aqueous environment, the
16 hardened implant may maintain a rubbery (non-rigid) composition with the
17 glass transition temperature being below 37°C.

18 Since the compositions often will be highly viscous prior to
19 implantation, when the composition is intended for implantation by injection,
20 the viscosity optionally may be modified by emulsifiers to obtain a gel
21 composition having a viscosity low enough to permit passage of the gel
22 composition through a needle. Also, pore formers and solubility modulators
23 of the beneficial agent may be added to the implant systems to provide
24 desired release profiles from the implant systems, along with typical

1 pharmaceutical excipients and other additives that do not change the
2 beneficial aspects of the present invention. The addition of a solubility
3 modulator to the implant system may enable the use of a solvent having a
4 solubility of 7% or greater in the implant system with minimal burst and
5 sustained delivery under particular circumstances. However, it is presently
6 preferred that the implant system utilize at least one solvent having a
7 solubility in water of less than 7% by weight, whether the solvent is present
8 alone or as part of a solvent mixture. It has also been discovered that when
9 mixtures of solvents which include a solvent having 7% or less by weight
10 solubility in water and one or more miscible solvents, optionally having
11 greater solubility, are used, implant systems exhibiting limited water uptake
12 and minimal burst and sustained delivery characteristics are obtained.

13 Definitions

14 The term "beneficial agent" means an agent that effects a desired
15 beneficial, often pharmacological, effect upon administration to a human or an
16 animal, whether alone or in combination with other pharmaceutical excipients
17 or inert ingredients.

18 The term "AUC" means the area under the curve obtained from an *in*
19 *vivo* assay in a subject by plotting blood plasma concentration of the
20 beneficial agent in the subject against time, as measured from the time of
21 implantation of the composition, to a time "*t*" after implantation. The time *t* will
22 correspond to the delivery period of beneficial agent to a subject.

23 The term "burst index" means, with respect to a particular composition
24 intended for systemic delivery of a beneficial agent, the quotient formed by

1 dividing (i) the AUC calculated for the first twenty-four hours after implantation
2 of the composition into a subject divided by the number 24, by (ii) the AUC
3 calculated for the time period of delivery of beneficial agent, divided by the
4 number of hours in the total duration of the delivery period.

5 The phrase "dissolved or dispersed" is intended to encompass all
6 means of establishing a presence of beneficial agent in the gel composition
7 and includes dissolution, dispersion, suspension and the like.

8 The term "systemic " means, with respect to delivery or administration
9 of a beneficial agent to a subject, that beneficial agent is detectable at a
10 biologically-significant level in the blood plasma of the subject.

11 The term "local " means, with respect to delivery or administration of a
12 beneficial agent to a subject, that beneficial agent is delivered to a localized
13 site in the subject but is not detectable at a biologically-significant level in the
14 blood plasma of the subject.

15 The term "gel vehicle" means the composition formed by mixture of the
16 polymer and solvent in the absence of the beneficial agent.

17 The term "prolonged period" means a period of time over which
18 release of a beneficial agent from the implant of the invention occurs, which
19 will generally be about one week or longer, and preferably about 30 days or
20 longer.

21 The term "initial burst" means, with respect to a particular composition
22 of this invention, the quotient obtained by dividing (i) the amount by weight of
23 beneficial agent released from the composition in a predetermined initial
24 period of time after implantation, by (ii) the total amount of beneficial agent

1 that is to be delivered from an implanted composition. It is understood that
2 the initial burst may vary depending on the shape and surface area of the
3 implant. Accordingly, the percentages and burst indices associated with
4 initial burst described herein are intended to apply to compositions tested in a
5 form resulting from dispensing of the composition from a standard syringe.

6 The term "solubility modulator" means, with respect to the beneficial
7 agent, an agent that will alter the solubility of the beneficial agent, with
8 reference to polymer solvent or water, from the solubility of beneficial agent in
9 the absence of the modulator. The modulator may enhance or retard the
10 solubility of the beneficial agent in the solvent or water. However, in the case
11 of beneficial agents that are highly water soluble, the solubility modulator will
12 generally be an agent that will retard the solubility of the beneficial agent in
13 water. The effects of solubility modulators of the beneficial agent may result
14 from intereactions of the solubility modulator with the solvent, or with the
15 beneficial agent itself, such as by the formation of complexes, or with both.
16 For the purposes hereof, when the solubility modulator is "associated" with
17 the beneficial agent, all such interactions or formations as may occur are
18 intended. Solubility modulators may be mixed with the beneficial agent prior
19 to its combination with the viscous gel or may be added to the viscous gel
20 prior to the addition of the beneficial agent, as appropriate.

21 The term "subject" means, with respect to the administration of a
22 composition of the invention, an animal or a human being.

23 Since all solvents, at least on a molecular level, will be soluble in water
24 (i.e., miscible with water) to some very limited extent, the term "immiscible" as

1 used herein means that 7% or less by weight of the solvent is soluble in or
2 miscible with water. For the purposes of this disclosure, solubility values of
3 solvent in water are considered to be determined at 20°C. Since it is
4 generally recognized that solubility values as reported may not always be
5 conducted at the same conditions, solubility limits recited herein as percent
6 by weight miscible or soluble with water as part of a range or upper limit may
7 not be absolute. For example, if the upper limit on solvent solubility in water
8 is recited herein as "7% by weight", and no further limitations on the solvent
9 are provided, the solvent "triacetin", which has a reported solubility in water of
10 7.17 grams in 100 ml of water, is considered to be included within the limit of
11 7%. A solubility limit in water of less than 7% by weight as used herein does
12 not include the solvent triacetin or solvents having solubilities in water equal
13 to or greater than triacetin.

14 The polymer, solvent and other agents of the invention must be
15 biocompatible; that is they must not cause irritation or necrosis in the
16 environment of use. The environment of use is a fluid environment and may
17 comprise a subcutaneous or intramuscular portion or body cavity of a human
18 or animal.

19 Polymers that may be useful in the invention may be biodegradable
20 and may include, but are not limited to polylactides, polyglycolides,
21 polycaprolactones, polyanhydrides, polyamines, polyurethanes,
22 polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals,
23 polycarbonates, polyorthocarbonates, polyphosphazenes, succinates,
24 poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol,

1 polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and
2 mixtures thereof.

3 Presently preferred polymers are polylactides, that is, a lactic acid-
4 based polymer that can be based solely on lactic acid or can be a copolymer
5 based on lactic acid and glycolic acid which may include small amounts of
6 other comonomers that do not substantially affect the advantageous results
7 which can be achieved in accordance with the present invention. As used
8 herein, the term "lactic acid" includes the isomers L-lactic acid, D-lactic acid,
9 DL-lactic acid and lactide while the term "glycolic acid" includes glycolide.
10 Most preferred are poly(lactide-co-glycolide) copolymers, commonly referred
11 to as PLGA. The polymer may have a monomer ratio of lactic acid/glycolic
12 acid of from about 100:0 to about 15:85, preferably from about 60:40 to about
13 75:25 and an especially useful copolymer has a monomer ratio of lactic
14 acid/glycolic acid of about 50:50.

15 The lactic acid-based polymer has a number average molecular weight
16 of from about 1,000 to about 120,000, preferably from about 5,000 to about
17 30,000 as determined by gas phase chromatography. As indicated in
18 aforementioned U.S. Patent No. 5,242,910, the polymer can be prepared in
19 accordance with the teachings of U.S. Patent No. 4,443,340. Alternatively,
20 the lactic acid-based polymer can be prepared directly from lactic acid or a
21 mixture of lactic acid and glycolic acid (with or without a further comonomer)
22 in accordance with the techniques set forth in U.S. Patent No. 5,310,865.
23 The contents of all of these patents are incorporated by reference. Suitable
24 lactic acid-based polymers are available commercially. For instance, 50:50

1 lactic acid:glycolic acid copolymers having molecular weights of 5,000,
2 10,000, 30,000 and 100,000, preferably about 8,000 to 13,000, and most
3 preferably about 10,000, and a wide variety of end groups to alter
4 susceptibility to hydrolysis and subsequent breakdown of the polymer chain
5 are available from Boehringer Ingelheim (Petersburg, VA).

6 The biocompatible polymer is present in the gel composition in an
7 amount ranging from about 5 to about 80% by weight, preferably from about
8 30 to about 70% by weight and often 40 to 60% by weight of the viscous gel,
9 the viscous gel comprising the combined amounts of the biocompatible
10 polymer and the solvent. The solvent will be added to polymer in amounts
11 described below, to provide implantable or injectable viscous gels.

12 The solvent must be biocompatible, should form a viscous gel with the
13 polymer, and restrict water uptake into the implant. The solvent may be a
14 single solvent or a mixture of solvents exhibiting the foregoing properties.
15 The term "solvent", unless specifically indicated otherwise, means a single
16 solvent or a mixture of solvents. Suitable solvents will substantially restrict
17 the uptake of water by the implant and may be characterized as immiscible in
18 water, i.e., having a solubility in water of less than 7% by weight. Preferably,
19 the solvents are five weight percent or less soluble in water; more preferably
20 three weight percent or less soluble in water; and even more preferably one
21 weight percent or less soluble in water. Most preferably the solubility of the
22 solvent in water is equal to or less than 0.5 weight percent.

23 Water miscibility may be determined experimentally as follows: Water
24 (1-5 g) is placed in a tared clear container at a controlled temperature, about

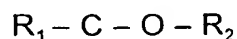
1 20°C, and weighed, and a candidate solvent is added dropwise. The solution
2 is swirled to observe phase separation. When the saturation point appears to
3 be reached, as determined by observation of phase separation, the solution
4 is allowed to stand overnight and is re-checked the following day. If the
5 solution is still saturated, as determined by observation of phase separation,
6 then the percent (w/w) of solvent added is determined. Otherwise more
7 solvent is added and the process repeated. Solubility or miscibility is
8 determined by dividing the total weight of solvent added by the final weight of
9 the solvent/water mixture. When solvent mixtures are used, for example 20%
10 triacetin and 80% benzyl benzoate, they are pre-mixed prior to adding to the
11 water.

12 Solvents useful in this invention are generally less than 7% water
13 soluble by weight as described above. Solvents having the above solubility
14 parameter may be selected from the lower alkyl and aralkyl esters of aryl
15 acids such as benzoic acid, the phthalic acids, salicylic acid, lower alkyl
16 esters of citric acid, such as triethyl citrate and tributyl citrate and the like, and
17 aryl, aralkyl and lower alkyl ketones. Among preferred solvents are those
18 having solubilities within the foregoing range selected from (i) compounds
19 having the following structural formulas :

20

O

21



1 and (i)



4 in which R_1 is aryl or aralkyl, R_2 is lower alkyl or aralkyl, and R_1 and R_2 are
5 optionally the same or different, with the proviso that when each of R_1 and R_2
6 are lower alkyl, the total carbon atoms in R_1 and R_2 combined are 4 or more,
7 and (ii) lower alkyl and aralkyl esters of phthalic acid, isophthalic acid and
8 terephthalic acid and (iii) lower alkyl and aralkyl esters of citric acid. For the
9 purposes hereof, lower alkyl means straight or branched chain hydrocarbons
10 having 1-6 carbon atoms, optionally substituted with non-interfering
11 substituents; aralkyl means (lower alkyl)phenyl, e.g., benzyl, phenethyl, 1-
12 phenylpropyl, 2-phenylpropyl, and the like wherein the alkyl moiety contains
13 from 1-6 carbon atoms; and aryl means phenyl, optionally substituted by non-
14 interfering substituents. Many of the solvents useful in the invention are
15 available commercially (Aldrich Chemicals, Sigma Chemicals) or may be
16 prepared by conventional esterification of the respective arylalkanoic acids
17 using acid halides, and optionally esterification catalysts, such as described in
18 US Patent No. 5,556,905, which is incorporated herein by reference, and in
19 the case of ketones, oxidation of their respective secondary alcohol
20 precursors.

21 Art recognized benzoic acid derivatives from which solvents having the
22 requisite solubility may be selected include: 1,4-cyclohexane dimethanol
23 dibenzoate, diethylene glycol dibenzoate, dipropylene glycol dibenzoate,

1 polypropylene glycol dibenzoate, propylene glycol dibenzoate, diethylene
2 glycol benzoate and dipropylene glycol benzoate blend, polyethylene glycol
3 (200) dibenzoate, iso decyl benzoate, neopentyl glycol dibenzoate, glyceryl
4 tribenzoate, pentaerythritol tetrabenzoate, cumylphenyl benzoate, trimethyl
5 pentanediol dibenzoate.

6 Art recognized phthalic acid derivatives from which solvents having the
7 requisite solubility may be selected include: Alkyl benzyl phthalate, bis-
8 cumyl-phenyl isophthalate, dibutoxyethyl phthalate, dimethyl phthalate,
9 dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diisobutyl phthalate,
10 butyl octyl phthalate, diisoheptyl phthalate, butyl octyl phthalate, diisononyl
11 phthalate, nonyl undecyl phthalate, dioctyl phthalate, di-iso octyl phthalate,
12 dicapryl phthalate, mixed alcohol phthalate, di-(2-ethylhexyl) phthalate, linear
13 heptyl, nonyl, phthalate, linear heptyl, nonyl, undecyl phthalate, linear nonyl
14 phthalate, linear nonyl undecyl phthalate, linear dinoyl, didecyl phthalate
15 (diisodecyl phthalate), diundecyl phthalate, ditridecyl phthalate,
16 undecyldodecyl phthalate, decyltridecyl phthalate, blend (50/50) of dioctyl and
17 didecyl phthalates, butyl benzyl phthalate, and dicyclohexyl phthalate.

18 Preferred solvents include the lower alkyl and aralkyl esters of the aryl
19 acids described above. Representative acids are benzoic acid and the
20 phthalic acids, such as phthalic acid, isophthalic acid, and terephthalic acid.
21 Most preferred solvents are derivatives of benzoic acid and include, but are
22 not limited to, methyl benzoate, ethyl benzoate, n-propyl benzoate, isopropyl
23 benzoate, butyl benzoate, isobutyl benzoate, sec-butyl benzoate, tert-butyl

1 benzoate, isoamyl benzoate and benzyl benzoate, with benzyl benzoate
2 being most especially preferred. Preferred solvent mixtures are those in
3 which benzyl benzoate is the primary solvent, and mixtures formed of benzyl
4 benzoate and either triacetin, tributyl citrate, triethyl citrate or N-methyl-2-
5 pyrrolidone. Preferred mixtures are those in which benzyl benzoate is
6 present by weight in an amount of 50% or more, more preferably 60% or
7 more and most preferably 80% or more of the total amount of solvent present.
8 Especially preferred mixtures are those of 80/20 mixtures by weight of benzyl
9 benzoate/triacetin and benzyl benzoate/N-methyl-2-pyrrolidone.

10 It has been surprisingly found that the solvents described above
11 having a miscibility in water of less than 7% by weight may be mixed with one
12 or more additional miscible solvents ("component solvents"). Component
13 solvents compatible and miscible with the primary solvent may have a higher
14 miscibility with water and the resulting mixtures may still exhibit significant
15 restriction of water uptake into the implant. Such mixtures will be referred to
16 as "component solvent mixtures." Useful component solvent mixtures may
17 exhibit solubilities in water greater than the primary solvents themselves,
18 typically between 0.1 weight percent and up to and including 50 weight
19 percent, preferably up to and including 30 weight percent, and most
20 preferably up to and including 10 weight percent, without detrimentally
21 affecting the restriction of water uptake exhibited by the implants of the
22 invention. Especially preferred are component solvent mixtures having a
23 solubility in water of about 0.1% to about 7% by weight.

1 Component solvents useful in component solvent mixtures are those
2 solvents that are miscible with the primary solvent or solvent mixture, and
3 include, but are not limited, to triacetin, diacetin, tributyrin, triethyl citrate,
4 tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides,
5 triethyl phosphate, diethyl phthalate, diethyl tartrate, mineral oil, polybutene,
6 silicone fluid, glycerin, ethylene glycol, polyethylene glycol, octanol, ethyl
7 lactate, propylene glycol, propylene carbonate, ethylene carbonate,
8 butyrolactone, ethylene oxide, propylene oxide, N-methyl-2-pyrrolidone, 2-
9 pyrrolidone, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl
10 ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam,
11 decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one, and
12 mixtures thereof.

13 In an especially preferred embodiment, the primary solvent is selected
14 from lower alkyl and aralkyl esters of benzoic acid and the polymer is a lactic-
15 acid based polymer, most preferably PLGA, having a number average
16 molecular weight of between about 8,000 to about 13,000, preferably about
17 10,000. Presently, the most preferred solvents are benzyl benzoate and the
18 lower alkyl esters of benzoic acid. The benzoic acid esters may be used
19 alone or in a mixture with other miscible solvents, e.g., triacetin, as described
20 herein. Implants are prepared as viscous gels in which the beneficial agent is
21 dissolved or dispersed substantially throughout, and such compositions are
22 useful both for systemic and local administration of beneficial agent, whether
23 or not initial burst is an important consideration. Additionally, use of esters of
24 benzoic acid provides increased control of water migration resulting in

1 increased stability of beneficial agent. The low water uptake, i.e., limited
2 water migration into the gel composition after implantation, permits the
3 practitioner of the invention to limit beneficial agent transfer by diffusion and
4 enhance control of the delivery profile of the beneficial agent by controlling
5 the bioerosion characteristics of the polymer. The preferred compositions
6 allow beneficial agent to be loaded into the interior of the polymer at levels
7 that are above that required to saturate the beneficial agent in water, thereby
8 facilitating zero order release of beneficial agent. Additionally, the preferred
9 compositions may provide viscous gels that have a glass transition
10 temperature that is less than 37°C, such that the gel remains non-rigid for a
11 period of time after implantation of 24 hours or more.

12 The solvent or solvent mixture is capable of dissolving the polymer to
13 form a viscous gel that can maintain particles of the beneficial agent
14 dissolved or dispersed and isolated from the environment of use prior to
15 release. The compositions of the present invention provide implants having a
16 low burst index. Water uptake is controlled by the use of a solvent or
17 component solvent mixture that solublizes or plasticizes the polymer but
18 substantially restricts uptake of water into implant.

19 The importance of restriction of water uptake can be appreciated by
20 reference to Figures 4A-4B illustrating bulk water uptake for various
21 compositions as a function of time and Table 1 illustrating representative
22 formulations for which burst indices have been determined.

23 Water uptake was determined for various polymer vehicles, i.e., 50%
24 polymer-50% solvent compositions, in the absence of beneficial agent. As

1 shown in Figure 4A, water uptake by a gel vehicle formed with the more water
2 miscible solvent N-methyl-2-pyrrolidone (NMP) is higher than that for any
3 other solvent-polymer combination, by about a factor of four or more. Water
4 uptake for the combination of 80% benzyl benzoate and 20% NMP by weight
5 in the solvent portion of the vehicle is less than a third that of NMP alone.
6 Implants with benzyl benzoate take up the least water, whether compared to
7 the other solvents alone or as mixtures with benzyl benzoate. Additionally, it
8 can be seen that the 80/20 mixture of benzyl benzoate and triacetin takes up
9 less than 10% water on a weight basis, and exhibits less water uptake than
10 triacetin alone. Figure 4B provides a comparison of various solvents alone
11 and demonstrates again the advantages of the benzoic acid esters,
12 particularly that of benzyl benzoate. A relative comparison of the water
13 uptake for the various solvents and the burst indices reproduced in the
14 foregoing Table 1 show a correlation between low water uptake values and
15 low burst indices. Gel compositions of this invention may take up 25 % or
16 less of their bulk weight in water within the first 7 days, 30% in the first 14
17 days and 40% in the first 21 days, as tested in the water migration assay
18 described herein.

19

20

Table 1

Solvent	Water Miscibility	Depot Gel ¹	Polymer ²	Zinc acetate (mM)	Process ³	Animal No.	Burst Index
Benzyl Benzoate	insol. in water (Merck)	D	PLGA-502	0	L	7 8	4.2 2.4
		K	PLGA-502	0	SD	21 22	3.6 2.4
		E	PLGA-502	7.5	L	9 10	4.5 2.3
		L	PLGA-502	7.5	SD	23 24	2.6 2.1
		F	PLGA-502	15	L	11 12	1.5 2.0
		F	PLGA-502	15	L	25 26	2.2 0.64
Triacetin	7% sol. in water (Merck)	A	PLGA-502	0	L	1 2	8.5 13
		I	PLGA-502	0	SD	17 18	12 10
		B	PLGA-502	7.5	L	3 4	4.1 2.1
		J	PLGA-502	7.5	SD	19 20	6.3 3.5
		C	PLGA-502	15	L	5 6	4.8 3.5
NMP	misc. with water (Merck)	G	PLGA-502	0	L	13 14	13 14
		H	PLGA-502	15	L	15 16	6.1 5.5

¹ All depot gels contained 10% hGH

² For all depot gels, hGH was loaded into (50/50) solvent / polymer vehicles

³ L = Lyophilized; SD = Spray-dried

In addition to the control of water uptake and associated initial burst by choice of solvent, agents that modulate the water solubility of the beneficial agent can also be utilized in conjunction with the preferred solvents to control burst of beneficial agent from the implant. Burst indices and percent of beneficial agent released in the first twenty-four

1 hours after implantation may be reduced by one-third to two-thirds or more by the use of
2 solubility modulators associated with the beneficial agent. Such modulators are typically
3 coatings, substances that form complexes or otherwise associate with or stabilize the
4 beneficial agent such as metallic ions, other stabilizing agents, waxes, lipids, oils, non-
5 polar emulsions, and the like. Use of such solubility modulators may permit the use of
6 more highly water soluble solvents or mixtures and achieve burst indices of 8 or less for
7 systemic applications, or with respect to local applications, release of beneficial agent in
8 the first 24 hours after implantation of not greater than 20% of the beneficial agent
9 administered. Preferably that release will be not greater than 15% and more preferably
10 not greater than 10%.

11 Limited water uptake by the compositions of this invention can often provide the
12 opportunity to prepare compositions without solubility modulators when in other
13 compositions such modulators would be necessary. For example with reference to
14 Table 1, suitable burst indices are obtained for a composition of PLGA, benzyl benzoate
15 and human growth hormone without the presence of Zn ion. Similar results may be
16 obtained with other beneficial agents, such as the interferons, including interferon alpha-
17 2a, interferon alpha-2b and consensus interferon.

18 In instances where the choice of solvent and polymer result in compositions
19 severely restricting water uptake by themselves, it may be desirable to add osmotic
20 agents or other agents and hydroattractants that facilitate water uptake to desired levels.
21 Such agents may be, for example, sugars and the like, and are well known in the art.

1 finger-like pores in the surface of implants formed using prior art processes.
2 Typically, a composition of the present invention takes the form of a
3 substantially, homogeneous, sponge-like gel, with the pores in the interior of
4 the implant being much the same as the pores on the surface of the implant.
5 Compositions of the present invention retain their gel-like consistency over a
6 longer period than do prior art devices and permit beneficial agent to be
7 delivered over a prolonged period. This is possible since the implants of the
8 present invention generally have a glass transition temperature, T_g , of less
9 than body temperature of the subject, e.g. 37°C for humans. Because of the
10 immiscibility of the solvents that are useful in this invention with water, water
11 uptake by the implant is restricted and the pores that do form tend to
12 resemble a closed cell structure without significant numbers of larger pores or
13 pores extending from the surface into the interior of the implant being open at
14 the surface of the implant. Furthermore, the surface pores offer only a limited
15 opportunity for water from body fluids to enter the implant immediately after
16 implantation, thus controlling the burst effect. Since the compositions often
17 will be highly viscous prior to implantation, when the composition is intended
18 for implantation by injection, the viscosity optionally may be modified by the
19 use of viscosity-reducing, miscible solvents or the use of emulsifiers, or by
20 heating to obtain a gel composition having a viscosity or shear resistance low
21 enough to permit passage of the gel composition through a needle.

22 The limit on the amount of beneficial agent released in the first 24
23 hours that is either desired or required will depend on circumstances such as
24 the overall duration of the delivery period, the therapeutic window for the

1 beneficial agent, potential adverse consequences due to overdosing, cost of
2 beneficial agent, and the type of effect desired, e.g., systemic or local.

3 Preferably, 20% or less of the beneficial agent will be released in the first 24
4 hours after implantation, where the percentage is based on the total amount
5 of beneficial agent to be delivered over the duration of the delivery period.

6 Typically, higher percentages of release in the first 24 hours can be tolerated
7 if the duration of the delivery period is relatively short, e.g., less than 7-14
8 days, or if the beneficial agent has a wide therapeutic window with little
9 likelihood of side effects, or if the beneficial agent acts locally.

10 Depending on the particular solvent or solvent mixture selected, the
11 polymer and beneficial agent, and optionally solubility modulators of the
12 beneficial agent, the compositions of the present invention intended for
13 systemic delivery may provide a gel composition having a burst index of 8 or
14 less, preferably 6 or less, more preferably 4 or less and most preferably 2 or
15 less. Compositions of PLGA with solvents having a miscibility in water of less
16 than 7% by weight, optionally combined with the other solvents, providing
17 implants intended for systemic delivery of beneficial agent having a burst
18 index of 10 or less, preferably 7 or less, more preferably 5 or less and most
19 preferably 3 or less, are particularly advantageous. The use of solvent
20 mixtures as discussed herein can be particularly advantageous as a means of
21 providing sufficient plasticizing of the polymer to obtain viscous gel formation
22 and at the same time meet the desired burst indices and percentage release
23 objectives of the compositions of the invention.

1 Compositions intended for local delivery of beneficial agent are formed
2 in the same manner as those intended for systemic use. However, because
3 local delivery of beneficial agent to a subject will not result in detectable
4 plasma levels of beneficial agent, such systems have to be characterized by
5 a percentage of beneficial agent released in a predetermined initial period,
6 rather than a burst index as defined herein. Most typically, that period will be
7 the first 24 hours after implantation and the percentage will be equal to the
8 amount by weight of the beneficial agent released in the period (e.g. 24
9 hours) divided by the amount by weight of the beneficial agent intended to be
10 delivered in the duration of the delivery period; multiplied by the number 100.
11 Compositions of the present invention will have initial bursts of 20% or less,
12 preferably 15% or less, most preferably 10% or less, for most applications.
13 Especially preferred are implant systems having initial bursts of 5% or less.

14 In many instances, it may be desirable to reduce the initial burst of
15 beneficial agent during local administration to prevent adverse effects. For
16 example, implants of the invention containing chemotherapeutic agents are
17 suitable for direct injection into tumors. However, many chemotherapeutic
18 agents may exhibit toxic side effects when administered systemically.
19 Consequently, local administration into the tumor may be the treatment
20 method of choice. It is necessary, however, to avoid administration of a large
21 burst of the chemotherapeutic agent if it is possible that such agent would
22 enter the vascular or lymphatic systems where it may exhibit side affects.
23 Accordingly, in such instances the implantable systems of the present
24 invention having limited burst as described herein are advantageous.

1 The solvent or solvent mixture is typically present in an amount of from
2 about 95 to about 20% by weight and is preferably present in an amount of
3 from about 70 to about 30% by weight and often 60-40% by weight of the
4 viscous gel, i.e., the combined amounts of the polymer and the solvent. The
5 viscous gel formed by mixing the polymer and the solvent typically exhibits a
6 viscosity of from about 1,000 to about 200,000 poise, preferably from about
7 5,000 to about 50,000 poise measured at a 1.0 sec^{-1} shear rate and 25°C
8 using a Haake Rheometer at about 1-2 days after mixing is completed.
9 Mixing the polymer with the solvent can be achieved with conventional low
10 shear equipment such as a Ross double planetary mixer for from about 10
11 minutes to about 1 hour, although shorter and longer periods may be chosen
12 by one skilled in the art depending on the particular physical characteristics of
13 the composition being prepared. Since it is often desirable to administer the
14 implant as an injectable composition, a countervailing consideration when
15 forming implants that are viscous gels is that the polymer/solvent/beneficial
16 agent composition have sufficiently low viscosity in order to permit it to be
17 forced through a small diameter, e.g., 18-20 gauge needle. If necessary,
18 adjustment of viscosity of the gel for injection can be accomplished with
19 emulsifying agents as described herein. Yet, such compositions should have
20 adequate dimensional stability so as to remain localized and be able to be
21 removed if necessary. The particular gel or gel-like compositions of the
22 present invention satisfy such requirements.

23 If the polymer composition is to be administered as an injectable gel,
24 the level of polymer dissolution will need to be balanced with the resulting gel

1 viscosity, to permit a reasonable force to dispense the viscous gel from a
2 needle, and the potential burst effect. Highly viscous gels enable the
3 beneficial agent to be delivered without exhibiting a significant burst effect,
4 but may make it difficult to dispense the gel through a needle. In those
5 instances, an emulsifying agent may optionally be added to the composition.
6 Also, since the viscosity may generally be lowered as the temperature of the
7 composition increases, it may be advantageous in certain applications to
8 reduce the viscosity of the gel by heating to provide a more readily injectable
9 composition.

10 For instance, as shown in Figure 1, a gel prepared from 40% by weight
11 of a 50:50 lactic acid:glycolic polymer and 60% by weight of triacetin required
12 about 40 psig to dispense the gel through a standard 20 gauge needle at 2
13 cc/min while a gel prepared from the same amount of polymer with 60% by
14 weight of N-methyl-2-pyrrolidone required only about 8 psig. Figure 1 further
15 shows that when the emulsifying agent (in this case 33% by weight of a 10%
16 ethanol solution) is added to the viscous gel according to the invention, the
17 dispense force needed is only about 2 psig. The shear thinning
18 characteristics of the depot gel compositions of the present invention allow
19 them to be readily injected into an animal including humans using standard
20 gauge needles without requiring undue dispensing pressure.

21 When the emulsifying agent is mixed with the viscous gel formed from
22 the polymer and the solvent using conventional static or mechanical mixing
23 devices, such as an orifice mixer, the emulsifying agent forms a separate
24 phase composed of dispersed droplets of microscopic size that typically have

1 an average diameter of less than about 100 microns. The continuous phase
2 is formed of the polymer and the solvent. The particles of the beneficial agent
3 may be dissolved or dispersed in either the continuous phase or the droplet
4 phase. In the resulting thixotropic composition, the droplets of emulsifying
5 agent elongate in the direction of shear and substantially decrease the
6 viscosity of the viscous gel formed from the polymer and the solvent. For
7 instance, with a viscous gel having a viscosity of from about 5,000 to about
8 50,000 poise measured at 1.0 sec^{-1} at 25°C , one can obtain a reduction in
9 viscosity to less than 100 poise when emulsified with a 10% ethanol/water
10 solution at 25°C as determined by Haake Rheometer.

11 When used, the emulsifying agent typically is present in an amount
12 ranging from about 5 to about 80%, preferably from about 20 to about 60%
13 and often 30 to 50% by weight based on the amount of the injectable depot
14 gel composition, that is the combined amounts of polymer, solvent,
15 emulsifying agent and beneficial agent. Emulsifying agents include, for
16 example, solvents that are not fully miscible with the polymer solvent or
17 solvent mixture. Illustrative emulsifying agents are water, alcohols, polyols,
18 esters, carboxylic acids, ketones, aldehydes and mixtures thereof. Preferred
19 emulsifying agents are alcohols, propylene glycol, ethylene glycol, glycerol,
20 water, and solutions and mixtures thereof. Especially preferred are water,
21 ethanol, and isopropyl alcohol and solutions and mixtures thereof. The type
22 of emulsifying agent affects the size of the dispersed droplets. For instance,
23 ethanol will provide droplets that have average diameters that can be on the

1 order of ten times larger than the droplets obtained with an isotonic saline
2 solution containing 0.9% by weight of sodium chloride at 21°C.

3 Figure 3 shows the viscosities at different shear rates using water
4 alone and an aqueous mixture containing 10% by volume of ethanol at a
5 weight ratio of 2:1 (gel:emulsifying agent) using a viscous gel formed from
6 50% by weight of a 50:50 lactic acid:glycolic acid copolymer and 50% by
7 weight of triacetin compared to the viscosities of the viscous gel without
8 emulsifying agent.

9 It is to be understood that the emulsifying agent does not constitute a
10 mere diluent that reduces viscosity by simply decreasing the concentration of
11 the components of the composition. The use of conventional diluents can
12 reduce viscosity, but can also cause the burst effect mentioned previously
13 when the diluted composition is injected. In contrast, the injectable depot
14 composition of the present invention can be formulated to avoid the burst
15 effect by selecting the solvent and emulsifying agent so that once injected
16 into place, the emulsifying agent has little impact on the release properties of
17 the original system.

18 Since the implant systems of the present invention preferably are
19 formed as viscous gels, the means of administration of the implants is not
20 limited to injection, although that mode of delivery may often be preferred.
21 Where the implant will be administered as a leave-behind product, it may be
22 formed to fit into a body cavity existing after completion of surgery or it may
23 be applied as a flowable gel by brushing or palleting the gel onto residual

1 tissue or bone. Such applications may permit loading of beneficial agent in
2 the gel above concentrations typically present with injectable compositions.

3 The beneficial agent can be any physiologically or pharmacologically
4 active substance or substances optionally in combination with
5 pharmaceutically acceptable carriers and additional ingredients such as
6 antioxidants, stabilizing agents, permeation enhancers, etc. that do not
7 substantially adversely affect the advantageous results that can be attained
8 by the present invention. The beneficial agent may be any of the agents
9 which are known to be delivered to the body of a human or an animal and
10 that are preferentially soluble in water rather than in the polymer-dissolving
11 solvent. These agents include drug agents, medicaments, vitamins,
12 nutrients, or the like. Included among the types of agents which meet this
13 description are lower molecular weight compounds, proteins, peptides,
14 genetic material, nutrients, vitamins, food supplements, sex sterilants, fertility
15 inhibitors and fertility promoters.

16 Drug agents which may be delivered by the present invention include
17 drugs which act on the peripheral nerves, adrenergic receptors, cholinergic
18 receptors, the skeletal muscles, the cardiovascular system, smooth muscles,
19 the blood circulatory system, synaptic sites, neuroeffector junctional sites,
20 endocrine and hormone systems, the immunological system, the reproductive
21 system, the skeletal system, autacoid systems, the alimentary and excretory
22 systems, the histamine system and the central nervous system. Suitable
23 agents may be selected from, for example, proteins, enzymes, hormones,
24 polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins,

1 polypeptides, steroids, analgesics, local anesthetics, antibiotic agents, anti-
2 inflammatory corticosteroids, ocular drugs and synthetic analogs of these
3 species.

4 Examples of drugs which may be delivered by the composition of the
5 present invention include, but are not limited to prochlorperzine edisylate,
6 ferrous sulfate, aminocaproic acid, mecamlamine hydrochloride,
7 procainamide hydrochloride, amphetamine sulfate, methamphetamine
8 hydrochloride, benzamphetamine hydrochloride, isoproterenol sulfate,
9 phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride,
10 pilocarpine hydrochloride, atropine sulfate, scopolamine bromide,
11 isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride,
12 methylphenidate hydrochloride, theophylline choline, cephalixin
13 hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate,
14 phenoxybenzamine, thiethylperzine maleate, anisindone, diphenadione
15 erythryl tetranitrate, digoxin, isofluorophate, acetazolamide, methazolamide,
16 bendroflumethiazide, chlorpromazine, tolazamide, chlormadinone acetate,
17 phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl
18 sulfisoxazole, erythromycin, hydrocortisone, hydrocorticosterone acetate,
19 cortisone acetate, dexamethasone and its derivatives such as
20 betamethasone, triamcinolone, methyltestosterone, 17-S-estradiol, ethinyl
21 estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17 α -
22 hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel,
23 norethindrone, norethisterone, norethindrone, progesterone, norgesterone,
24 norethynodrel, aspirin, indomethacin, naproxen, fenoprofen, sulindac,

1 indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol,
2 alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine,
3 methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate,
4 ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac,
5 ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem,
6 milrinone, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen,
7 fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal,
8 nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine,
9 tiapamil, gallopamil, amlodipine, mioflazine, lisinopril, enalapril, enalaprilat,
10 captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine, tetratolol,
11 minoxidil, chlordiazepoxide, diazepam, amitriptyline, and imipramine. Further
12 examples are proteins and peptides which include, but are not limited to,
13 bone morphogenic proteins, insulin, colchicine, glucagon, thyroid stimulating
14 hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin,
15 corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic
16 gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine
17 somatotropin, oxytocin, vasopressin, GRF, somatostatin, lypressin,
18 pancreozymin, luteinizing hormone, LHRH, LHRH agonists and antagonists,
19 leuprolide, interferons such as interferon alpha-2a, interferon alpha-2b, and
20 consensus interferon, interleukins, growth hormones such as human growth
21 hormone and its derivatives such as methionine-human growth hormone and
22 des-phenylalanine human growth hormone, bovine growth hormone and
23 porcine growth hormone, fertility inhibitors such as the prostaglandins, fertility
24 promoters, growth factors such as insulin-like growth factor, coagulation

1 factors, human pancreas hormone releasing factor, analogs and derivatives
2 of these compounds, and pharmaceutically acceptable salts of these
3 compounds, or their analogs or derivatives.

4 The present invention also finds application with chemotherapeutic
5 agents for the local application of such agents to avoid or minimize systemic
6 side effects. Gels of the present invention containing chemotherapeutic
7 agents may be injected directly into the tumor tissue for sustained delivery of
8 the chemotherapeutic agent over time. In some cases, particularly after
9 resection of the tumor, the gel may be implanted directly into the resulting
10 cavity or may be applied to the remaining tissue as a coating. In cases in
11 which the gel is implanted after surgery, it is possible to utilize gels having
12 higher viscosities since they do not have to pass through a small diameter
13 needle. Representative chemotherapeutic agents that may be delivered in
14 accordance with the practice of the present invention include, for example,
15 carboplatin, cisplatin, paclitaxel, BCNU, vincristine, camptothecin, etoposide,
16 cytokines, ribozymes, interferons, oligonucleotides and oligonucleotide
17 sequences that inhibit translation or transcription of tumor genes, functional
18 derivatives of the foregoing, and generally known chemotherapeutic agents
19 such as those described in U.S. Patent 5,651,986. The present application
20 has particular utility in the sustained delivery of water soluble
21 chemotherapeutic agents, such as for example cisplatin and carboplatin and
22 the water soluble derivatives of paclitaxel. Those characteristics of the
23 invention that minimize the burst effect are particularly advantageous in the
24 administration of water soluble beneficial agents of all kinds, but particularly

1 those compounds that are clinically useful and effective but may have
2 adverse side effects.

3 To the extent not mentioned above, the beneficial agents described in
4 aforementioned U.S. Patent No. 5,242,910 can also be used. One particular
5 advantage of the present invention is that materials, such as proteins, as
6 exemplified by the enzyme lysozyme, and cDNA, and DNA incorporated into
7 vectors both viral and nonviral, which are difficult to microencapsulate or
8 process into microspheres can be incorporated into the compositions of the
9 present invention without the level of degradation caused by exposure to high
10 temperatures and denaturing solvents often present in other processing
11 techniques.

12 The beneficial agent is preferably incorporated into the viscous gel
13 formed from the polymer and the solvent in the form of particles typically
14 having an average particle size of from about 0.1 to about 100 microns,
15 preferably from about 1 to about 25 microns and often from 2 to 10 microns.
16 For instance, particles having an average particle size of about 5 microns
17 have been produced by spray drying or freeze drying an aqueous mixture
18 containing 50% sucrose and 50% chicken lysozyme (on a dry weight basis)
19 and mixtures of 10-20% hGH and 15-30 mM zinc acetate. Such particles
20 have been used in certain of the examples illustrated in the figures.
21 Conventional lyophilization processes can also be utilized to form particles of
22 beneficial agents of varying sizes using appropriate freezing and drying
23 cycles.

1 To form a suspension or dispersion of particles of the beneficial agent
2 in the viscous gel formed from the polymer and the solvent, any conventional
3 low shear device can be used such as a Ross double planetary mixer at
4 ambient conditions. In this manner, efficient distribution of the beneficial
5 agent can be achieved substantially without degrading the beneficial agent.

6 The beneficial agent is typically dissolved or dispersed in the
7 composition in an amount of from about 1 to about 50% by weight, preferably
8 in an amount of from about 5 to about 30% and often 10 to 20% by weight of
9 the combined amounts of the polymer, solvent and beneficial agent.
10 Depending on the amount of beneficial agent present in the composition, one
11 can obtain different release profiles and burst indices. More specifically, for a
12 given polymer and solvent, by adjusting the amounts of these components
13 and the amount of the beneficial agent, one can obtain a release profile that
14 depends more on the degradation of the polymer than the diffusion of the
15 beneficial agent from the composition or vice versa. In this respect, at lower
16 beneficial agent loading rates, one generally obtains a release profile
17 reflecting degradation of the polymer wherein the release rate increases with
18 time. At higher loading rates, one generally obtains a release profile caused
19 by diffusion of the beneficial agent wherein the release rate decreases with
20 time. At intermediate loading rates, one obtains combined release profiles so
21 that if desired, a substantially constant release rate can be attained. In order
22 to minimize burst, loading of beneficial agent on the order of 30% or less by
23 weight of the overall gel composition, i.e., polymer, solvent and beneficial
24 agent, is preferred, and loading of 20% or less is more preferred.

1 Release rates and loading of beneficial agent will be adjusted to
2 provide for therapeutically-effective delivery of the beneficial agent over the
3 intended sustained delivery period. Preferably, the beneficial agent will be
4 present in the polymer gel at concentrations that are above the saturation
5 concentration of beneficial agent in water to provide a drug reservoir from
6 which the beneficial agent is dispensed. While the release rate of beneficial
7 agent depends on the particular circumstances, such as the beneficial agent
8 to be administered, release rates on the order of from about 0.1 to about 100
9 micrograms/day, preferably from about 1 to about 10 micrograms per day, for
10 periods of from about 7 to about 90 days can be obtained. Greater amounts
11 may be delivered if delivery is to occur over shorter periods. Generally,
12 higher release rate is possible if a greater burst can be tolerated. In
13 instances where the gel composition is surgically implanted, or used as a
14 "leave behind" depot when surgery to treat the disease state or another
15 condition is concurrently conducted, it is possible to provide higher doses that
16 would normally be administered if the implant was injected. Further, the dose
17 of beneficial agent may be controlled by adjusting the volume of the gel
18 implanted or the injectable gel injected. As can be seen from Figure 2 with
19 respect to lysozyme, with more highly viscous systems, one can avoid a burst
20 effect and deliver on the order of 1% by weight of the beneficial agent in the
21 composition during the first day.

22 Figures 5A and 5B illustrate representative release profiles of human
23 growth hormone ("hGH") obtained in rats from preferred compositions of this
24 invention. The benefits of benzyl benzoate are apparent in that comparison.

1 The hGH-benzyl benzoate implant shows a lower burst and a nearly zero
2 order sustained release of hGH over the release period for both the case
3 wherein the hGH is not stabilized (Figure 5A) and the case in which hGH is
4 stabilized with zinc ions (Figure 5B).

5 Other components may be present in the gel composition, to the extent
6 they are desired or provide useful properties to the composition, such as
7 polyethylene glycol, hydroscopic agents, stabilizing agents, pore forming
8 agents, and others. When the composition includes a peptide or a protein
9 that is soluble in or unstable in an aqueous environment, it may be highly
10 desirable to include a solubility modulator, that may, for example, be a
11 stabilizing agent, in the composition. Various modulating agents are
12 described in U.S. Patent Nos. 5,654,010 and 5,656,297 which are
13 incorporated herein by reference. In the case of hGH, for example, it is
14 preferable to include an amount of a salt of a divalent metal, preferably zinc.
15 Examples of such modulators and stabilizing agents, which may form
16 complexes with the beneficial agent or associate to provide the stabilizing or
17 modulated release effect, include metal cations, preferably divalent, present
18 in the composition as magnesium carbonate, zinc carbonate, calcium
19 carbonate, magnesium acetate, magnesium sulfate, zinc acetate, zinc sulfate,
20 zinc chloride, magnesium chloride, magnesium oxide, magnesium hydroxide,
21 other antacids, and the like. The amounts of such agents used will depend
22 on the nature of the complex formed, if any, or the nature of the association
23 between the beneficial agent and the agent. Molar ratios of solubility

1 modulator or stabilizing agent to beneficial agent of about 100:1 to 1:1,
2 preferably 10:1 to 1:1, typically can be utilized.

3 Pore forming agents include, biocompatible materials that when
4 contacted with body fluids dissolve, disperse or degrade to create pores or
5 channels in the polymer matrix. Typically, organic and non-organic materials
6 that are water soluble such as sugars (e.g., sucrose, dextrose), water soluble
7 salts (e.g., sodium chloride, sodium phosphate, potassium chloride, and
8 sodium carbonate), water soluble solvents such as N-methyl-2-pyrrolidone
9 and polyethylene glycol and water soluble polymers (e.g.,
10 carboxymethylcellulose, hydroxypropylcellulose, and the like) can conveniently
11 be used as pore formers. Such materials may be present in amounts varying
12 from about 0.1% to about 100% of the weight of the polymer, but will typically
13 be less than 50% and more typically less than 10-20% of the weight of
14 polymer.

15 Compositions of this invention without beneficial agent are useful for
16 wound healing, bone repair and other structural support purposes.

17 To further understand the various aspects of the present invention, the
18 results set forth in the previously described Figures were obtained in
19 accordance with the following examples.

20 Example 1

21 Lysozyme particles were made by spray drying 50% sucrose and 50%
22 chicken lysozyme (on a dry weight basis).

23 A viscous gel material was prepared by heating 60% by weight of
24 triacetin with 40% by weight of a 50:50 lactic acid:glycolic acid copolymer to

1 37°C overnight. The viscous gel was allowed to cool to room temperature.
2 The lysozyme particles were added to the viscous gel in a ratio of 20:80
3 lysozyme particles:gel (by weight). The combination was mixed for 5
4 minutes. Immediately prior to use, a 10% ethanol, 90% isotonic saline
5 solution was added as the emulsifying agent. The emulsifying agent
6 comprised 1/3 of the total injectable depot gel composition. The prepared
7 compositions were suitable for injection.

8 Figure 2 shows the in vitro release rates obtained from the
9 compositions described with regard to Figure 1. The gel prepared from 40%
10 by weight of a 50:50 lactic acid:glycolic polymer and 60% by weight triacetin
11 is thick and thus difficult to inject but shows little burst (less than 2% of the
12 beneficial agent is delivered in the first eight days). The gel prepared from
13 40% by weight of a 50:50 lactic acid:glycolic polymer and 60% by weight n-
14 methyl-2-pyrrolidone is thin and injectable but shows a large burst (greater
15 than 70% of the beneficial agent is delivered in the first eight days). The gel
16 prepared from 27% by weight of a 50:50 lactic acid:glycolic polymer, 40% by
17 weight triacetin and 33% by weight of a 10% ethanol, 90% isotonic saline
18 solution is thin and injectable and shows little burst (less than 10% of the
19 beneficial agent is delivered in the first eight days). In each case, lysozyme is
20 the beneficial agent and comprises 20% by weight of the combined beneficial
21 agent, polymer and solvent formulation.

22 Example 2 - hGH Particle Preparation

23 Human growth hormone (hGH) particles (optionally containing zinc
24 acetate) were prepared as follows:

hGH solution (5 mg/ml) solution in water (BresaGen Corporation, Adelaide, Australia) was concentrated to 10 mg/mL using a Concentration/Dialysis Selector diafiltering apparatus. The diafiltered hGH solution was then washed with 5 times volume of tris or phosphate buffer solution (pH 7.6). Particles of hGH were then formed by spray drying or lyophilization using conventional techniques. Phosphate buffer solutions (5 or 50 mM) containing hGH (5 mg/mL) and various levels of zinc acetate (0 to 30 mM) were spray-dried using a Yamato Mini Spraydryer set at the following parameters:

Spray Dryer Parameter	Setting
Atomizing Air	2 psi
Inlet Temperature	120°C
Aspirator Dial	7.5
Solution Pump	2-4
Main Air Valve	40-45 psi

hGH particles having a size range between 2 - 100 microns were obtained. Lyophilized particles were prepared from tris buffer solutions (5 or 50 mM: pH 7.6) containing hGH (5 mg/mL) and various levels of zinc acetate (0 to 30 mM) using a Durastop μ P Lyophilizer in accordance with the following freezing and drying cycles:

Freezing Cycle	Ramp down at 2.5 C/min to -30 C and hold for 30 minutes
	Ramp down at 2.5 C/min from -30 C to -50C and hold for 60 minutes
Drying Cycle	Ramp up at 0.5 C/min to 10 C and hold for 960 min
	Ramp up at 0.5 C/min to 20 C and hold for 480 min
	Ramp up at 0.5 C/min to 25 C and hold for 300 min
	Ramp up at 0.5 C/min to 30 C and hold for 300 min
	Ramp down at 0.5 C/min to 5 C and hold for 5000 min

hGH particles having a size range between 2 - 100 microns were obtained.

1 hGH Zinc Complexed Solution Preparation

2 Zinc acetate solutions were prepared with tris buffer and phosphate
3 buffer. Desired molar volumes of trizma hydrochloride and trizma base were
4 prepared separately
5 (5 or 50 mM). The pH of trizma base solution was measured, and the
6 corresponding trizma hydrochloride solution was added to adjust the pH of
7 the trizma base solution, resulting with a final pH of 7.6. The desired molar
8 volume of zinc acetate was added to the buffer solution. Desired molar
9 volumes of sodium phosphate monobasic and sodium phosphate dibasic
10 were prepared separately (5 or 50 mM). Sodium azide (0.2% w/w) was
11 added to each phosphate solution. The pH of the dibasic solution was
12 measured, and the corresponding monobasic solution was added to adjust
13 the pH of the dibasic solution, resulting with a final pH of 7.6. The desired
14 molar volume of zinc acetate was added to the buffer solution. Tris or
15 phosphate buffer containing zinc acetate was added to the diafiltered hGH
16 solution to achieve the final desired zinc acetate molar volume (between 5
17 and 30 mM). The final hGH concentration was 5 mg/mL.

18 Gel Vehicle Preparation

19 A glass vessel was tared on a Mettler PJ3000 top loader balance. Poly
20 (D,L-lactide-co-glycolide) 50:50 RESOMER® RG502 (PLGA-502) was weighed
21 into the glass vessel. The glass vessel containing PLGA-502 was tared and
22 the corresponding solvent was added. Amounts expressed as percentages for
23 various polymer/solvent combinations are set forth in Table 2 below. The
24 polymer/solvent mixture was manually stirred with a stainless steel square-tip

1 spatula, resulting in a sticky amber paste-like substance containing white
2 polymer particles. The vessel containing the polymer/solvent mixture was
3 sealed and placed in a temperature controlled incubator equilibrated to 39°C.
4 The polymer/solvent mixture was removed from the incubator when it appeared
5 to be a clear amber homogeneous gel. Incubation time intervals ranged from 1
6 to 4 days, depending on solvent and polymer type and solvent and polymer
7 ratios. Additional depot gel vehicles are prepared with the following polymers:
8 Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® L104, PLGA-L104, code no.
9 33007, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG206, PLGA-206,
10 code no. 8815, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER® RG502,
11 PLGA-502, code 0000366, Poly (D,L-lactide-co-glycolide) 50:50 RESOMER®
12 RG502H, PLGA-502H, code no. 260187, Poly (D,L-lactide-co-glycolide) 50:50
13 RESOMER® RG503, PLGA-503, code no. 0080765, Poly (D,L-lactide-co-
14 glycolide) 50:50 RESOMER® RG506, PLGA-506, code no. 95051, Poly (D,L-
15 lactide-co-glycolide) 50:50 RESOMER® RG755, PLGA-755, code no. 95037,
16 (Boehringer Ingelheim Chemicals, Inc., Petersburg, VA), and the following
17 solvents or mixtures: glyceryl triacetate (Eastman Chemical Co., Kingsport,
18 TN), benzyl benzoate ("BB"), ethyl benzoate ("EB"), methyl benzoate ("MB"),
19 triacetin ("TA"), and triethyl citrate ("TC") (Aldrich Chemical Co., St Louis, MO).
20 When solvent combinations were used, for example 20% triacetin and 80%
21 benzyl benzoate, the solvent mixture was directly added to the pre-weighed dry
22 polymer. Typical polymer molecular weights were in the range of 14,400 -
23 39,700 (M_w) [6,400-12,200 (M_n)]. Representative gel vehicles are described in
24 Table 2 below.

Table 2: Gel Vehicles

Solvent/ Polymer	Solvent	Polymer	Amount Solvent	Amount Polymer	Gel Weight	Ratio
50/50	BB	PLGA-502	5 g	5 g	10 g	1.0
50/50	TA / BB Mixture	PLGA-502	5 g	5 g	10 g	1.0
60/40	TA / BB Mixture	PLGA-502	6 g	4 g	10 g	1.5
70/30	TA / BB Mixture	PLGA-502	7 g	3 g	10 g	2.3
80/20	TA / BB Mixture	PLGA-502	8 g	2 g	10 g	4.0
50/50	EB	PLGA-502	5 g	5 g	10 g	1.0
50/50	TA / EB Mixture	PLGA-502	5 g	5 g	10 g	1.0
50/50	BB	PLGA-502	25 g	25 g	50 g	1.0
55/45	BB	PLGA-502	27.5 g	22.5 g	50 g	1.2
50/50	BB	PLGA-502	50 g	50 g	100 g	1.0
50/50	TA / BB Mixture	PLGA-502	50 g	50 g	100 g	1.0
50/50	BB	PLGA-502H	5 g	5 g	10 g	1.0
50/50	BB	PLGA-503	50 g	50 g	100 g	1.0

Drug Loading

Spray-dried or lyophilized hGH particles (10 - 20% w/w), with and without zinc acetate, prepared as above were added to a specified clear amber depot gel vehicle and blended manually until the dry powder was wetted completely. Then, the milky light yellow particle/gel mixture was thoroughly blended by conventional mixing using a Caframo mechanical stirrer with an attached square-tip metal spatula. Resulting formulations are illustrated in Tables 3 and 4 below. "L" identifies lyophilized hGH particles and "SD" identifies spray dried hGH particles. Final homogenous gel formulations were transferred to 3, 10 or 30 cc disposable syringes for storage or dispensing.

Table 3: In Vivo hGH

Formulation	Polymer		Solvent		Drug Particle			Trizma Buffer (mM)
	Level	PLGA	Level	Type	Level	Process	Zinc Level (mM)	
A	45%	502	45%	TA	10%	L	0	50
B	45%	502	45%	TA	10%	L	7.5	50
C	45%	502	45%	TA	10%	L	15	50
D	45%	502	45%	BB	10%	L	0	50
E	45%	502	45%	BB	10%	L	7.5	50
F	45%	502	45%	BB	10%	L	15	50
G	45%	502	45%	NMP	10%	L	0	50
H	45%	502	45%	NMP	10%	L	15	50
I	45%	502	45%	TA	10%	SD	0	50
J	45%	502	45%	TA	10%	SD	7.5	50
K	45%	502	45%	BB	10%	SD	0	50
L	45%	502	45%	BB	10%	SD	7.5	50

Table 4: In Vivo hGH (zinc level in all cases was 15 mM)

Formulation	Polymer		Solvent		Drug Particle		Trizma Buffer (mM)
	Level	PLGA	Level	Type	Level	Process	
F	45%	502	45%	BB	10%	L	50
N	45%	502	45%	80%BB/20%TA	10%	L	5
P	45%	502H	45%	TA	10%	L	5
Q	45%	502H	45%	BB	10%	L	5
R	45%	502	45%	EB	10%	L	5
S	45%	502	45%	TC	10%	L	5
T	40%	502	40%	BB	20%	L	5
W	45%	502-2	45%	BB	10%	L	5
X	45%	502	45%	TA	10%	L	5

Example 3 - Lysozyme In Vitro Studies

Lysozyme from chicken egg white (Sigma Chemical Co., St Louis, MO)

in vitro release studies were used to test different vehicle formulations with the highly water soluble solvent NMP and the less soluble solvents triacetin and benzyl benzoate useful in the present invention. A depot gel formulation was dispensed from a 3 cc disposable syringe and weighed onto a Delrin™ cup platform or a 250 μ mesh 1 square inch polypropylene screen. Then, the cup or screen containing a depot gel formulation was immersed into a plastic

1 cup or screen containing a depot gel formulation was immersed into a plastic
2 vial containing 10 mL of receptor buffer. A snap-on lid was placed onto the
3 plastic vial to prevent evaporation. The vial containing the depot gel
4 formulation was immersed into a Haake shaking water bath equilibrated to
5 37°C. At each time point, forceps were used to transfer Delrin™ cup
6 platforms or polypropylene screen platforms containing depot gel formulations
7 to new plastic vials containing 10 mL of receptor buffer. Disposable transfer
8 pipettes were used to transfer receptor samples to HPLC vials. The receptor
9 buffer was phosphate buffered saline, PBS, adjusted to pH 7 containing
10 sodium azide (0.2%). Receptor buffers contained tween-80 (0.1%) for most
11 cases. Collection intervals were typically 2, 4, 8 hours, 1, 2, 3, 4, 7, 10 days,
12 and 2, 3, 4, 5, 6, 7, 8 weeks. All receptor samples were analyzed for
13 lysozyme concentration using a gradient elution Reverse-Phase High
14 Performance Liquid Chromatography (RP-HPLC) assay with a refrigerated
15 autosampler (4°C). Results indicated that the compositions of the present
16 invention using benzyl benzoate and benzyl benzoate solvent mixtures
17 exhibited substantially less burst of lysozyme than that exhibited by the gel
18 compositions formed with NMP.

19 Example 4 - In Vitro Water Content Studies

20 The same procedure was used as described in Example 3 for in vitro drug
21 release using the Delrin™ cup platform, except the entire cup platform
22 containing the depot gel vehicle was removed, blotted dry, and placed in a
23 dry plastic vial at specified time intervals. The receptor solution was sterile
24 water and replaced at each time interval for the remaining samples. Initial

1 and final depot gel vehicle weights were recorded to observe weight change.

2 Water content was obtained from depot gel vehicles using a Karl Fischer

3 Apparatus, Mitsubishi Moisture Meter CA-06 equipped with Vaporizer VA-06.

4 Results are illustrated in Figures 4A-4B for selected gels. Those results

5 demonstrate that gel compositions of this invention take up substantially less

6 water than gel compositions formed with NMP alone.

7 Example 5 - hGH In Vivo Studies

8 In vivo studies in rats were performed following an open protocol to determine

9 serum levels of hGH upon systemic administration of hGH via the implant

10 systems of this invention. Depot gel hGH formulations, spray-dried (SD) or

11 lyophilized (L), were loaded into customized 0.5 cc disposable syringes.

12 Disposable 16 gauge needles were attached to the syringes and were heated

13 to 37°C using a circulator bath. Depot gel hGH formulations were injected

14 into rats and blood was drawn at specified time intervals. All serum samples

15 were stored at 4°C prior to analysis. Samples were analyzed for intact hGH

16 content using a radio immuno assay (RIA). Representative results for

17 triacetin and benzyl benzoate are illustrated in Figures 5A and 5B, and

18 demonstrate the superior control of burst by the compositions of the present

19 invention.

20 Example 6

21 Implant systems of this invention are prepared in accordance with

22 Example 2 with equivalent quantities of interferon alpha-2a and -2b,

23 consensus interferon, methionine human growth hormone, des-phenylalanine

24 human growth hormone, carboplatin and insulin-like growth factor. The

1 amount of the viscous gel containing drug administered to rats in accordance
2 with Example 5 is adjusted to take into account the relative biological activity
3 of the separate agents. The implant systems are implanted in rats to provide
4 systemic levels of active agent.

5 Example 7

6 Implant systems containing carboplatin are prepared according to
7 Example 6 and injected directly into solid tumors of tumor bearing rats. The
8 implant systems are suitable for local delivery of carboplatin to tumors.

9 Example 8

10 100 Mg implantable depots containing 0.5, 1.5 and 3 mg of interferon
11 alpha-2b, stabilized with 0.5, 1 and 2 mg of sucrose, respectively, and the
12 remainder being 50 mg benzyl benzoate and 45-49 mg of PLGA 502 as
13 applicable (number average molecular weight of about 10,000) are prepared
14 in accordance with Example 2 (without the addition of zinc). The implants
15 exhibit limited burst and are suitable for implantation. The implant systems
16 are implanted in rats to provide systemic levels of interferon alpha-2b.

17 In accordance with various aspects of the present invention, one or
18 more significant advantages can be obtained. More specifically, implantable
19 or injectable viscous gels containing beneficial agent for systemic and local
20 administration are obtained that exhibit low or minimal burst effect when
21 implanted. Furthermore, using simple processing steps, one can obtain a gel
22 composition that can be surgically implanted in an animal or injected into
23 place in an animal without surgery using a low dispensing force through
24 standard needles. Once in place, the composition will substantially avoid a

1 burst effect and provide the desired beneficial agent release profile.
2 Furthermore, once the beneficial agent has been fully administered, there is
3 no need to remove the composition since it is fully biodegradable. As a still
4 further advantage, the present invention avoids the use of microparticle or
5 microencapsulation techniques which can degrade certain beneficial agents,
6 like peptide and nucleic acid-based drugs and which microparticles and
7 microcapsules may be difficult to remove from the environment of use. Since
8 the viscous gel is formed without the need for water, temperature extremes,
9 or other solvents, suspended particles of beneficial agent remain dry and in
10 their original configuration, which contributes to the stability of thereof.
11 Further, since a mass is formed, the injectable depot gel composition may be
12 retrieved from the environment of use if desired.

13 The above-described exemplary embodiments are intended to be
14 illustrative in all respects, rather than restrictive, of the present invention.
15 Thus the present invention is capable of many variations in detailed
16 implementation that can be derived from the description contained herein by
17 a person skilled in the art. All such variations and modifications are
18 considered to be within the scope and spirit of the present invention as
19 defined by the following claims.

1 WE CLAIM:

2 1. A method of systemically administering a beneficial agent to a
3 subject which comprises implanting a system comprising a beneficial agent
4 dissolved or dispersed substantially throughout a viscous gel, the system
5 having a burst index of 8 or less.

6 2. The method of Claim 1 wherein the viscous gel comprises a
7 biocompatible polymer and a solvent.

8 3. The method of Claim 2 in which the viscous gel optionally includes
9 one or more of the following: an emulsifying agent, a pore former, a solubility
10 modulator for the beneficial agent and an osmotic agent.

11 4. The method of Claim 2 wherein the solvent comprises a solvent
12 having a miscibility in water of less than 7% by weight.

13 5. The method of Claim 4 wherein the solvent is selected from lower
14 alkyl and aralkyl esters of aryl acids; aryl, aralkyl and lower alkyl ketones; and
15 lower alkyl esters of citric acid.

16 6. The method of Claim 2 wherein the polymer is selected from the
17 group consisting of polylactides, polyglycolides, polycaprolactones,
18 polyanhydrides, polyamines, polyurethanes, polyesteramides,
19 polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates,
20 polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid),
21 poly(amino acids), polyvinylpyrrolidone, polyethylene glycol,
22 polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and
23 mixtures thereof.

1 7. The method of Claim 5 wherein the polymer is a lactic acid-based
2 polymer and the solvent is selected from lower alkyl and aralkyl esters of
3 benzoic acid.

4 8. A method of locally administering a beneficial agent to a subject
5 which comprises implanting a system comprising a beneficial agent dissolved
6 or dispersed substantially throughout a viscous gel, the system releasing
7 within 24 hours after implantation not greater than 20% by weight of the
8 amount of beneficial agent to be delivered over the duration of the delivery
9 period.

10 9. The method of Claim 8 wherein the viscous gel comprises a
11 biocompatible polymer and a solvent.

12 10. The method of Claim 9 in which the viscous gel optionally includes
13 one or more of the following: an emulsifying agent, a pore former, a solubility
14 modulator for the beneficial agent, and an osmotic agent.

15 11. The method of Claim 10 wherein the solvent comprises a solvent
16 having a miscibility in water of less than 7% by weight.

17 12. The method of Claim 11 wherein the solvent is selected from
18 lower alkyl and aralkyl esters of aryl acids; aryl, aralkyl and lower alkyl
19 ketones; and lower alkyl esters of citric acid.

20 13. The method of Claim 9 wherein the polymer is selected from the
21 group consisting of polylactides, polyglycolides, polycaprolactones,
22 polyanhydrides, polyamines, polyurethanes, polyesteramides,
23 polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates,
24 polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid),

1 poly(amino acids), polyvinylpyrrolidone, polyethylene glycol,
2 polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and
3 mixtures thereof.

4 14. The method of Claim 12 wherein the polymer is a lactic acid-
5 based polymer and the solvent is selected from lower alkyl and aralkyl esters
6 of benzoic acid.

7 15. A method of administering a beneficial agent to a subject in a
8 controlled manner approximating zero order release by implanting a gel
9 composition comprising a biocompatible polymer, a biocompatible solvent
10 having a solubility in water of less than 7%, and a beneficial agent, wherein
11 the loading of the beneficial agent in the interior of the polymer is above that
12 required to saturate the beneficial agent in water.

13 16. A method of administering a beneficial agent to a subject which
14 comprises implanting a system comprising a beneficial agent dissolved or
15 dispersed substantially throughout a viscous gel formed of a biocompatible
16 polymer and a solvent having a solubility in water of 7% or less, and a
17 solubility modulator of the beneficial agent, the system having a burst index of
18 8 or less.

19 17. The method of Claim 16 wherein the polymer is a lactic acid-
20 based polymer.

21 18. An implantable composition for the systemic delivery of a
22 beneficial agent to a subject wherein the composition comprises a polymer;
23 an amount of a solvent to form a viscous gel with the polymer, and a
24 beneficial agent dissolved or dispersed in the gel, wherein the solvent

1 comprises a single solvent or a mixture of solvents with at least one solvent
2 having a miscibility in water of less than 7% by weight and the total amount of
3 solvent constituting 40% or more by weight of the gel vehicle, said
4 composition having a burst index of 8 or less.

5 19. An implantable, biodegradable composition for the sustained
6 delivery of a beneficial agent to a subject wherein the composition comprises
7 a polymer; an effective plasticizing amount of a solvent to form a viscous gel
8 with the polymer; and a beneficial agent dissolved or dispersed in the gel,
9 wherein the solvent comprises a mixture of solvents with at least one solvent
10 in the mixture having a miscibility in water of less than 7% by weight.

11 20. The composition of Claim 19 wherein the miscibility in water of the
12 solvent mixture is 10% or less by weight.

13 21. An implantable, biodegradable composition for delivery of a
14 beneficial agent to a subject wherein the composition comprises a polymer;
15 an effective plasticizing amount of a solvent to form a viscous gel with the
16 polymer; and a beneficial agent dissolved or dispersed in the gel, wherein the
17 solvent comprises a single solvent or a mixture of solvents with at least one
18 solvent having a miscibility in water of less than 7% by weight selected from
19 lower alkyl and aralkyl esters of benzoic acid.

20 22. An implantable gel composition for delivery of a beneficial agent to
21 a subject comprising:

22 A) a biocompatible polymer;

1 D) an emulsifying agent;

2 E) a pore former;

3 F) a solubility modulator for the beneficial agent; and

4 G) an osmotic agent.

5 24. The composition of Claim 23 wherein R₁ is phenyl.

6 25. The composition of Claim 24 wherein R₂ is benzyl.

7 26. A method of preparing an injectable depot gel composition comprising:

8 A) mixing a biocompatible polymer and a solvent having a miscibility in water of
9 7% or less selected from lower alkyl and aralkyl esters of benzoic acid to form a
10 viscous gel;

11 B) dispersing or dissolving a beneficial agent, optionally associated with a
12 solubility modulator, in an emulsifying agent to form a beneficial agent containing
13 emulsifying agent; and

14 C) mixing the beneficial agent containing emulsifying agent with the viscous
15 gel, said beneficial agent containing emulsifying agent forming a dispersed droplet
16 phase in the viscous gel, and optionally,

17 D) mixing one or more of a pore former and an osmotic agent with said
18 viscous gel, to provide an injectable gel composition.

19 27. A gel composition for systemic administration comprising:

20 A) a biocompatible polymer;

21 B) a biocompatible solvent having a miscibility in water of less than 7%;

1 C) a beneficial agent selected from the group consisting of cDNA, DNA,
2 peptides, proteins and fragments and derivatives thereof, and optionally, one or more
3 of the following:

4 D) an emulsifying agent;

5 E) a pore former;

6 F) a solubility modulator for the beneficial agent; and

7 G) an osmotic agent.

8 wherein the composition has a burst index of less than 8.

9 28. A kit for administration of a beneficial agent to a subject comprising:

10 A) a biocompatible polymer;

11 B) a solvent having a miscibility in water of 7% or less by weight that is suitable
12 for dissolving the polymer and forming a viscous gel;

13 C) a beneficial agent; and optionally, one or more of the following:

14 D) an emulsifying agent;

15 E) a pore former;

16 F) a solubility modulator for the beneficial agent, optionally associated with the
17 beneficial agent; and

18 G) an osmotic agent;

19 wherein at least the beneficial agent, optionally associated with the solubility
20 modulator, is maintained separated from the solvent until the time of administration of
21 the beneficial agent to a subject.

22 29. An implantable composition for the systemic delivery of a beneficial agent
23 comprising a poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a

1 solvent to form a viscous gel with the polymer; and a beneficial agent selected from the
2 group consisting of cDNA, DNA, peptides, proteins and fragments and derivatives
3 thereof, said composition having a burst index of equal to or less than 8.

4 30. An implantable composition for the sustained delivery of a beneficial agent
5 comprising a poly(lactide-co-glycolide) copolymer; an effective plasticizing amount of a
6 solvent comprising a lower alkyl or aralkyl ester of benzoic acid to form a viscous gel
7 with the polymer; and a beneficial agent.

8 31. The composition of Claim 30 wherein the solvent has a miscibility in water
9 by weight of less than 7%.

10 32. The composition of Claim 30 wherein the solvent is benzyl benzoate.

11 33. The composition of Claim 30 comprising a solubility modulator of the
12 beneficial agent.

13 34. The composition of Claim 30 comprising a pore former.

14 35. The composition of Claim 30 comprising an emulsifying agent.

15 36. The composition of Claim 30 comprising an osmotic agent.

16 37. The composition of Claim 33 wherein the solubility modulator is selected
17 from salts of divalent metals.

18 38. The composition of Claim 34 in which the pore former is water soluble.

19 39. The composition of Claim 34 wherein the pore former is selected from group
20 consisting of water soluble sugars, salts, solvents and polymers.

21 40. The composition of Claim 35 in which the emulsifying agent is capable of
22 forming a dispersed droplet phase in said viscous gel.

1 41. The composition of Claim 35 in which the emulsifying agent is selected from
2 the group consisting of alcohols, propylene glycol, ethylene glycol, glycerol, water and
3 solutions and mixtures thereof.

4 42. The composition of Claim 35 wherein the emulsifying agent is selected from
5 the group consisting of ethanol, isopropyl alcohol, water, solutions thereof, and
6 mixtures thereof.

7 43. The composition of Claim 30 wherein the copolymer has a monomer ratio of
8 lactic acid to glycolic acid in the range of 100:0 to about 15:85.

9 44. The composition of Claim 30 wherein the copolymer has a number average
10 molecular weight of from 1,000 to 120,000.

11 45. The composition of Claim 30 wherein the solvent comprises a component
12 solvent miscible with the solvent.

13 46. The composition of Claim 45 wherein the component solvent is selected
14 from the group consisting of triacetin, diacetin, tributyrin, triethyl citrate, tributyl citrate,
15 acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides, triethyl phosphate, diethyl
16 phthalate, diethyl tartrate, mineral oil, polybutene, silicone fluid, glylcerin, ethylene
17 glycol, polyethylene glycol, octanol, ethyl lactate, propylene glycol, propylene
18 carbonate, ethylene carbonate, butyrolactone, ethylene oxide, propylene oxide, N-
19 methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, methyl acetate, ethyl acetate,
20 methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran,
21 caprolactam, decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one,
22 and mixtures thereof.

1 47. The composition of Claim 45 wherein the component solvent is selected
2 from the group consisting of triacetin and N-methyl-2-pyrrolidone, and mixtures thereof.

3 48. The composition of Claim 45 wherein the component solvent is triacetin.

4 49. The method of Claim 2 wherein the beneficial agent is present in an amount
5 of from 1 to 50% by weight of the combined amounts of the polymer, the solvent and
6 the beneficial agent.

7 50. The method of Claim 1 wherein the beneficial agent is cDNA, DNA, a
8 protein, a peptide, and derivatives or fragments thereof, or a chemotherapeutic agent.

9 51. The method of Claim 50 wherein the beneficial agent is human growth
10 hormone, methionine-human growth hormone, des-phenylalanine human growth
11 hormone, interferon alpha-2a, interferon alpha-2b, or consensus interferon.

12 52. The method of Claim 8 wherein the beneficial agent is cDNA, DNA, a
13 protein, a peptide, and derivatives or fragments thereof, or a chemotherapeutic agent.

14 53. The method of Claim 1 wherein the beneficial agent is released from the
15 system over a prolonged period.

16 54. The method of Claim 8 wherein the beneficial agent is released from the
17 system over a prolonged period.

18 55. The method of Claim 1 wherein the system is non-rigid after implantation.

19 56. The method of Claim 55 wherein the system maintains a glass transition
20 temperature below 37°C for at least 24 hours after implantation.

21 57. The method of Claim 9 wherein the system is non-rigid after implantation.

22 58. The method of Claim 57 wherein the system maintains a glass transition
23 temperature below 37°C for at least 24 hours after implantation.

1 59. The composition of Claim 18 wherein the gel remains non-rigid after
2 implantation.

3 60. The composition of Claim 59 wherein the gel maintains a glass transition
4 temperature below 37°C for at least 24 hours after implantation.

5 61. An implantable gel composition comprising a biocompatible polymer, a
6 biocompatible solvent forming a viscous gel with the polymer, and a beneficial agent,
7 the composition imbibing 40% or less of its bulk weight in water within the first 21 days
8 after implantation.

9 62. The composition of Claim 61 wherein the composition imbibes less than
10 30% of its bulk weight in water within the first 14 days after implantation.

11 63. The composition of Claim 62 wherein the composition imbibes less than
12 25% of its bulk weight in water within the first 7 days after implantation.

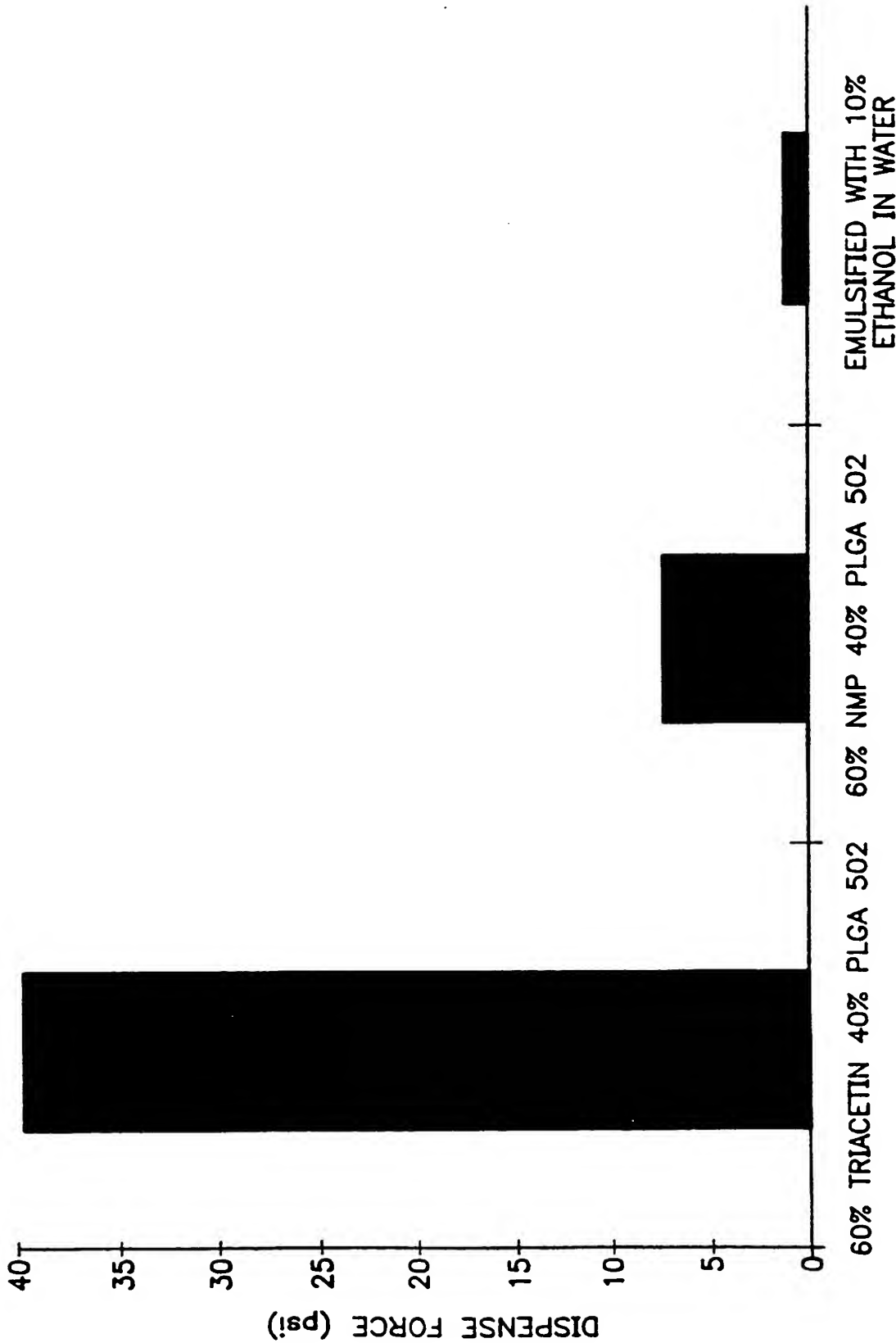


FIG. 1

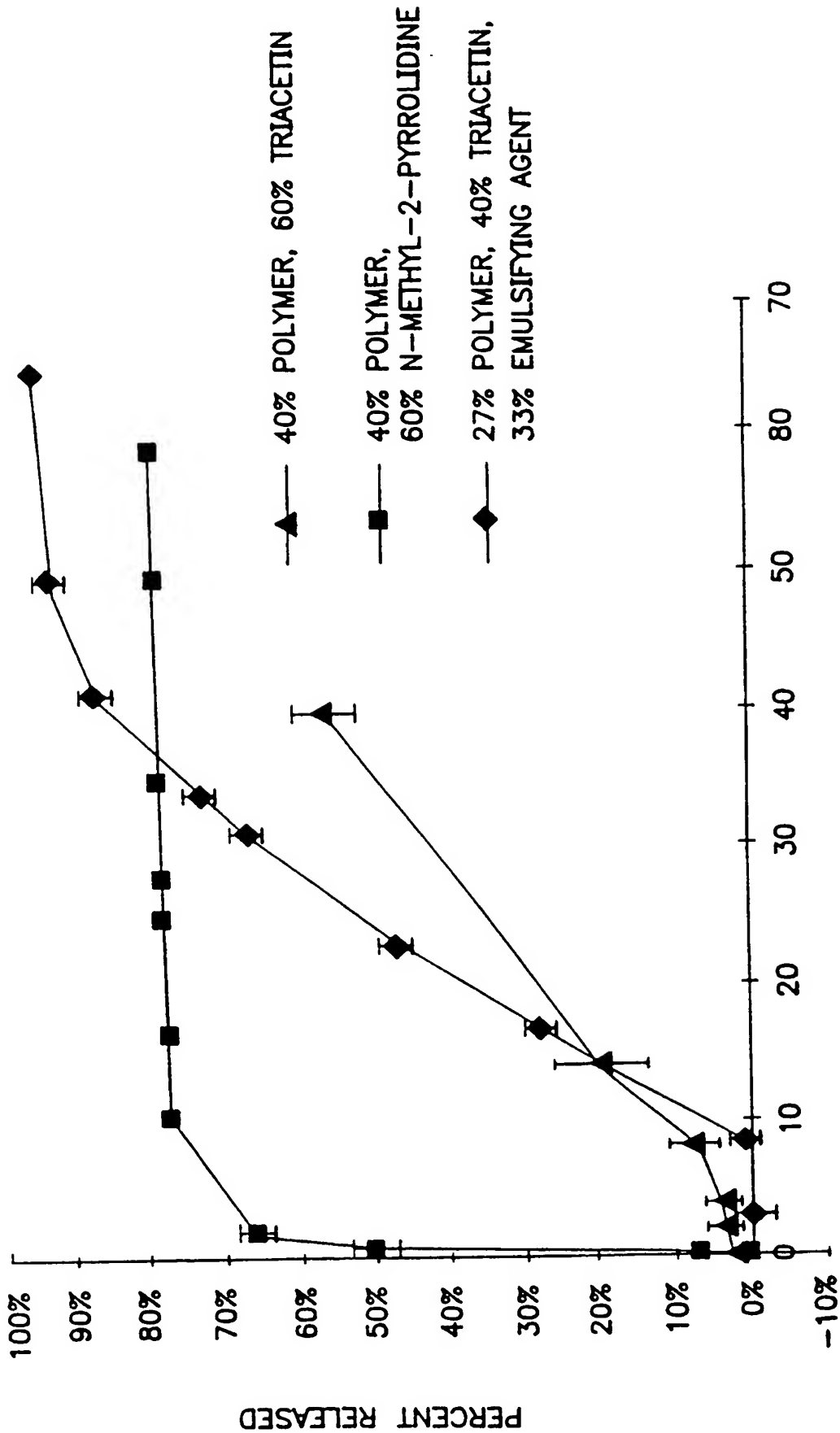


FIG. 2

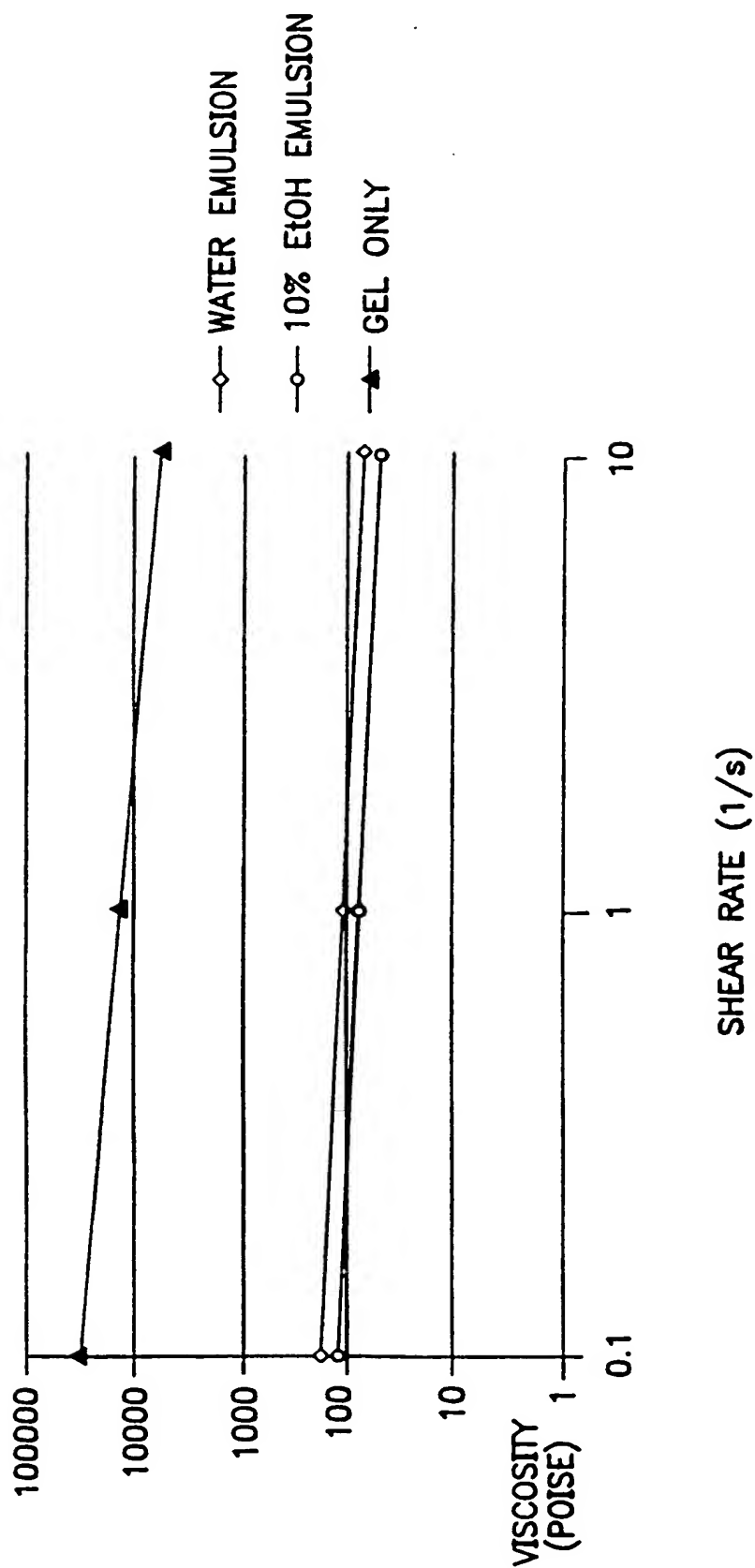


FIG. 3

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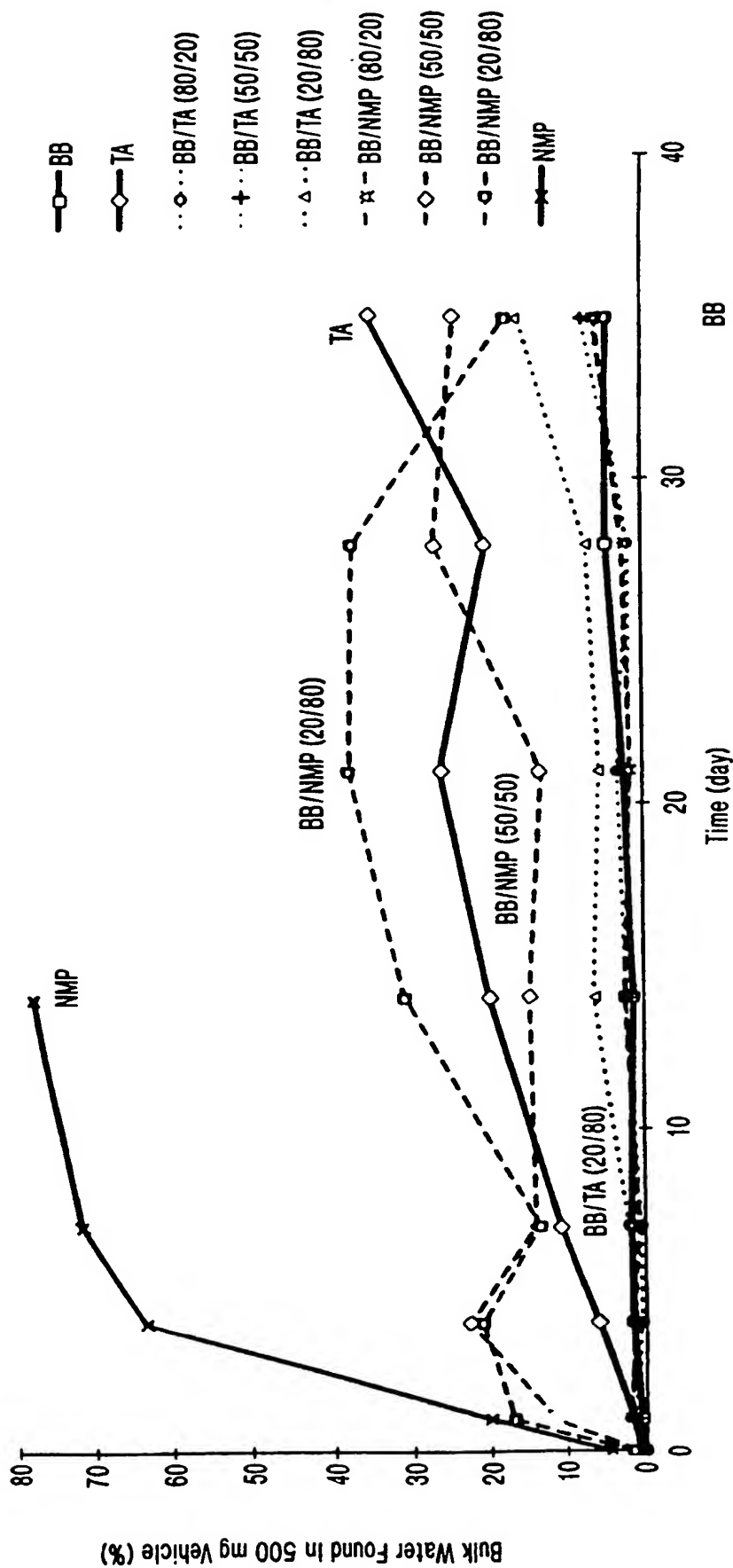


FIG. 4A

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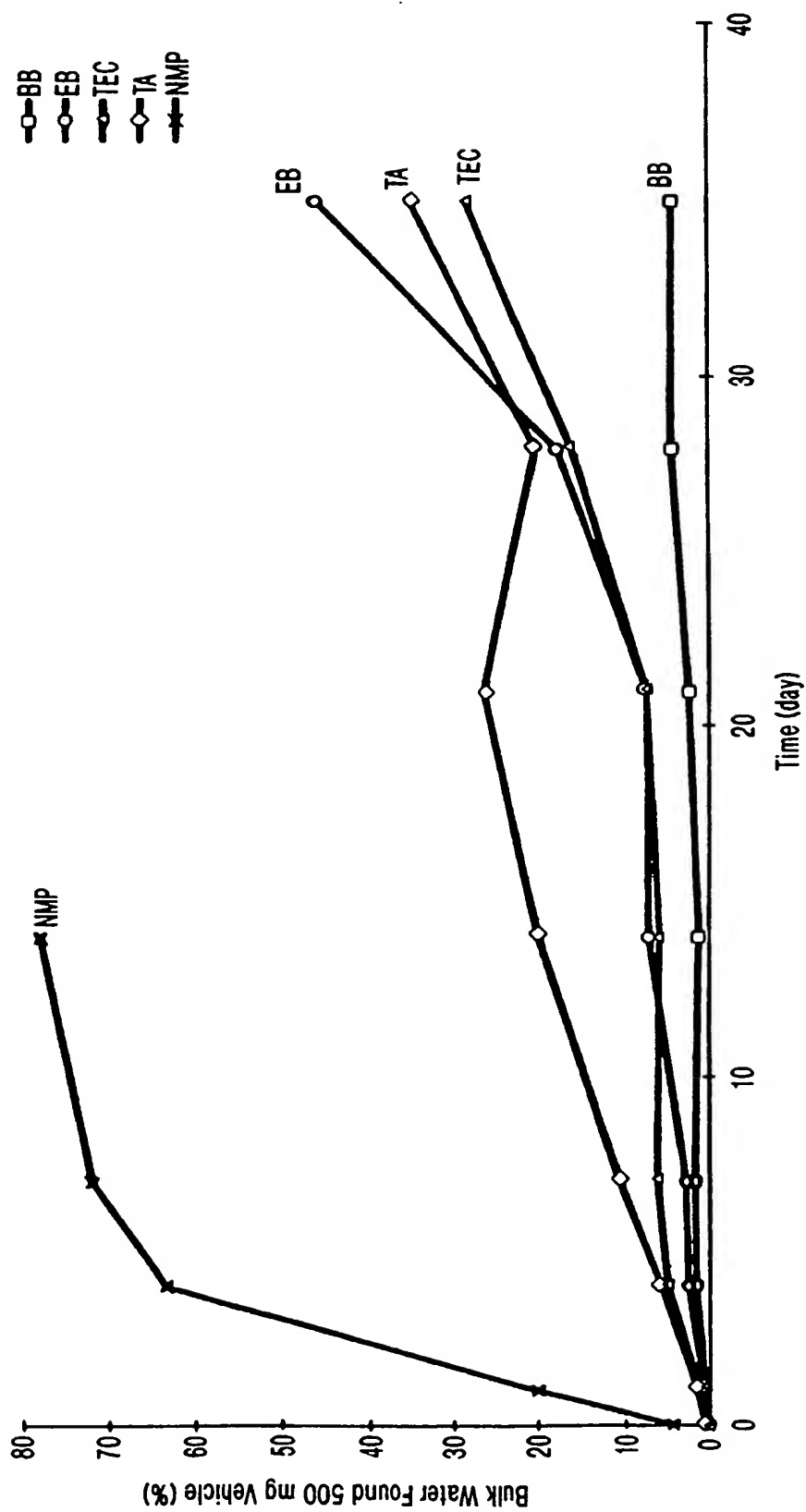


FIG. 4B

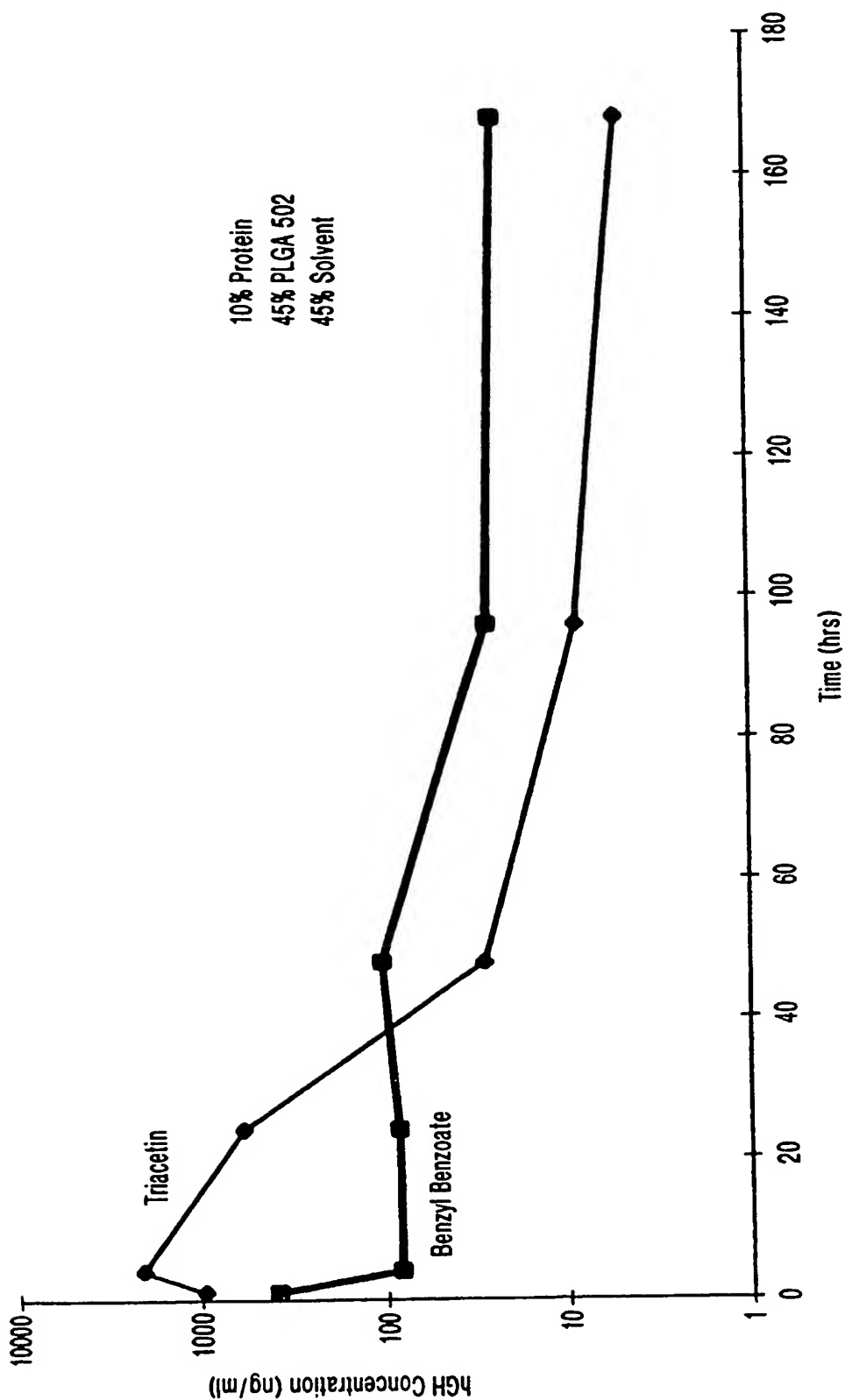


FIG. 5A

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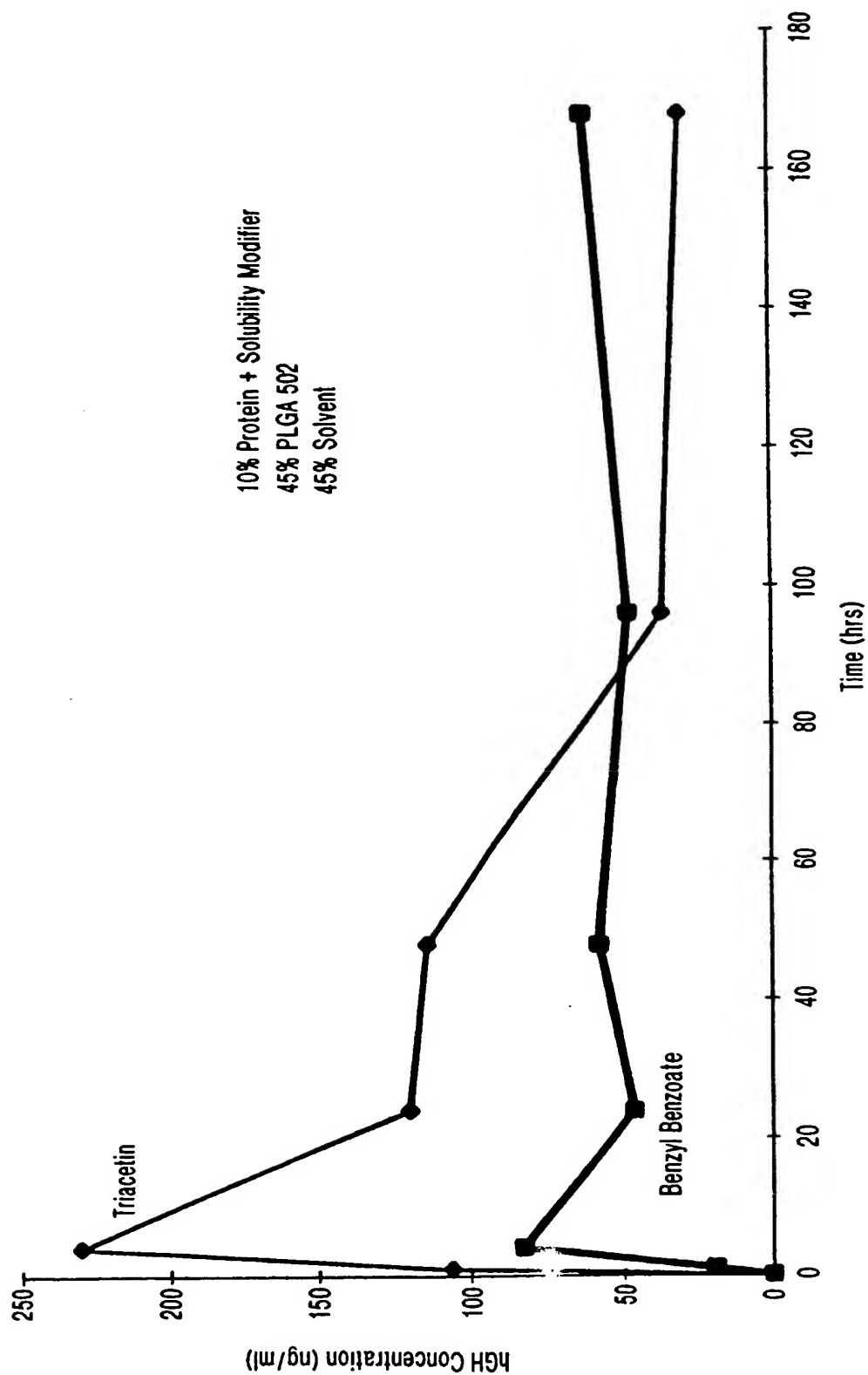


FIG. 5B



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 47/34	A3	(11) International Publication Number: WO 98/27963 (43) International Publication Date: 2 July 1998 (02.07.98)
(21) International Application Number: PCT/US97/23659 (22) International Filing Date: 18 December 1997 (18.12.97) (30) Priority Data: 60/033,439 20 December 1996 (20.12.96) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRODBECK, Kevin, J. [US/US]; 2383 South Court Street, Palo Alto, CA 94301 (US). GAYNOR-DUARTE, Ann, T. [US/US]; 13063 Broadway Terrace, Oakland, CA 94611 (US). SHEN, Theodore, T. [US/US]; 18 Dockside Circle, Redwood City, CA 94065 (US). (74) Agents: DHUEY, John, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 15 October 1998 (15.10.98)
(54) Title: GEL COMPOSITION AND METHODS (57) Abstract <p>Methods and compositions for systemically or locally administering by implantation a beneficial agent to a subject are described, and include, for example, compositions having burst indices of 8 or less for systemic applications and systems releasing 10 % or less of the total dose of beneficial agent in the first 24 hours after implantation for local applications. The compositions include a biocompatible polymer, a biocompatible solvent having low water miscibility that forms a viscous gel with the polymer and limits water uptake by the implant, and a beneficial agent.</p>		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23659

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/00 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 95 27481 A (ATRIX LABORATORIES INC., U.S.A.) 19 October 1995</p> <p>see claims 1-3, 7, 10-15, 19-27, 30 see page 4, line 26 - line 30 see page 14, line 3 - line 5 see page 14, line 22 - page 15, line 1 see page 18, line 33 - page 19, line 10 see page 26, line 21 - line 25 see page 30, line 12 - line 16</p> <p>---</p> <p>-/--</p>	<p>1-3, 5, 6, 8-10, 12, 13, 18-20, 27, 29, 49-55, 59</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

22 July 1998

Date of mailing of the inter

31.07.98

Name and mailing address of the ISA

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Scarponi, U

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23659

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 03768 A (SOUTHERN RESEARCH INSTITUTE, U.S.A.) 19 April 1990 cited in the application see claims 1-10, 27-37, 45 ---	1-6, 16-20, 27, 29, 49, 50, 53, 55
X	US 5 242 910 A (N.C.DAMANJ) 7 September 1993 cited in the application see claims see column 5, line 20 - column 27 see column 5, line 64 - line 67 see examples IV, V, VI ---	1-6, 15-20, 49, 50, 53, 55
X	EP 0 539 751 A (ATRIX LABORATORIES INC., U.S.A.) 5 May 1993 cited in the application see claims ---	1-6, 16-20, 27, 29, 49, 50, 53, 55
X, P	WO 97 15287 A (MACROMED INC., U.S.A.) 1 May 1997 see claims 1, 5, 8, 13-18, 34 see page 21, line 15 - line 18 see page 11, line 5 - line 21 see page 15, line 29 - page 16, line 9 see page 17, line 35 - line 37 see page 22, line 18 - line 24 see page 23, line 1 - line 12 ---	1-3, 6, 29, 49-51, 53, 55, 56
A	WO 91 05544 A (MEDINVENT, SE) 2 May 1991 see claims 1, 2, 10, 12-14, 18 see page 7, line 1 - line 3 see page 4, line 19 - line 31 ---	1-3, 6, 8, 15, 26, 28, 49, 53-55, 61
A	US 5 318 780 A (T.X.VIEGAS ET AL.) 7 June 1994 see claims --- -/--	1-3, 6, 8, 15, 26, 28, 49, 53-55.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23659

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP 0 640 647 A (COLLAGEN CORPORATION,U.S.A.) 1 March 1995</p> <p>see claims 1,3,5,44,47 see page 3, line 39 - line 41 see page 3, line 50 - line 52 see page 24, line 2 - line 5 see page 24, line 30 - line 34 -----</p>	<p>1-3,6,8, 15,26, 28,49, 53-55,61</p>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 23659

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-17, 49-58
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-17, 49-58 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

3T

International Application No	
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Information on patent family members

International Application No

PCT/US 97/23659

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